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Table of Contents.

TECHNIQUE OF ASPIRATION BIOPSY OF THE LIVER WITH REFERENCE TO ITS USE IN DIAGNOSIS AND PROGNOSIS.

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WITH AN APPENDIX ON HISTOLOGICAL TECHNIQUE

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DURING the past year the Clinical Research Unit of the Walter and Eliza Hall Institute has been investigating the problem of liver disease by clinical and biochemical studies. To aid this work it was decided to undertake aspiration biopsy of the liver, and this procedure, which is new to this country, has been found to be of such value for diagnosis and prognosis in properly selected cases that it has been decided to report the method in detail and briefly discuss its use.

Since it was first described by Lucatello[(1)] in Italy in 1895, aspiration biopsy has been carried out all over the world with varying reports regarding its usefulness and dangers. The modern era of this operation may be said to have begun in 1939, when Iversen and Roholm[(2)] published their results of 160 biopsies made without any fatalities. The technique used by these workers has been the basis for most successful studies, particularly in Britain and the Scandinavian countries. Van Beek and Baex[(3)] in 1943 reported 200 biopsies without any fatalities, and Dible, McMichael and Sherlock[(4)] and then Sherlock[(5)] report 245 biopsies with two fatalities (in both cases the prognosis was hopeless).

Despite these favourable results, it must not be thought that this is a procedure which can be undertaken lightly. On the contrary, there are certain rules that must be followed carefully if serious mishap is to be avoided.

Selection of Cases.

At the beginning of the present series, biopsy was performed only as an alternative to exploratory laparotomy in cases of persistent jaundice with equivocal clinical and biochemical findings, or to assess prognosis when there was clinical evidence of liver damage. With increased experience it is now used as an aid to diagnosis in most cases of jaundice, and in cases of liver disease in which the diagnosis still remains in doubt after full clinical and biochemical investigation. It is essential to have a cooperative patient, and for this reason biopsies have not been performed under general anæsthesia or on comatose patients. For the same reason highly excitable patients may present a problem for the operator, and they are best avoided by the inexperienced. More experience is required in cases of diffuse parenchymatous liver disease associated with jaundice, as it is in this type of case that the danger of hæmorrhage is most real.

Preparation of the Patient.

The two complications most to be feared are hæmorrhage from the liver and perforation of the bowel. As a routine measure, therefore, the prothrombin time is estimated on all patients several days beforehand, and unless this is at least 80% of normal, biopsy is delayed. If the figure is low, vitamin *K* is injected intramuscularly in a daily dose of five milligrammes, and a further estimation is made in a week. In all cases, however, vitamin *K* is given as a routine preparation each day for three days beforehand. A word of warning may be given here that these injections are very painful if not given intramuscularly, and they may worry the patient more than the actual biopsy.

[1] This work was aided by a grant from the National Health and Medical Research Council.

Should the prothrombin time not be made to rise to a satisfactory level by this means, transfusion of fresh blood may be used in the immediate pre-operative period if the necessity for biopsy is urgent. All patients should have their blood group determined, and a Casoni test to exclude hydatid disease is a necessary and additional safeguard.

To obviate the risk of perforation of an adherent or displaced loop of bowel, a plain X-ray film of the liver area is taken during full expiration and with the tube centred on the liver. This picture is prepared on the day of biopsy. It gives a clear outline of the hepatic shadow, and gas-filled coils of bowel are easily seen. It is also of help in fixing the position of the diaphragm if the liver is shrunken, and may even reveal a calcified cyst. In one case this X-ray film revealed bowel shadows as high as the eleventh intercostal space, where the bowel was adherent to the liver (Figure I). Of almost equal importance is the instruction of the patient for the operation if a successful biopsy is desired. The aim of the biopsy should be briefly explained and the importance of cooperation stressed. The patient must be assured that it will be a painless procedure. Usually preliminary sedation is better avoided, as it may interfere with full cooperation. To impress the patient with the fact that it is a minor procedure, it is desirable to perform the biopsy in the ward or ward annexe, and an unnecessary array of instruments is to be avoided.

A full surgical skin preparation is carried out from beneath the breast to the umbilicus, extending from the mid-line to the loin.

Instruments Required.

The Franseen needle (Figure II) obtained from America has been used in this series. This has an internal bore of one millimetre and is nine centimetres long. The point has three sharp cutting teeth, while the base has a locking device to fit the syringe. There is a sharp-pointed trocar to fit this needle. A 20-millilitre "Luer Lok" syringe with a dental grip is the most useful, since this allows of adequate suction by fitting tightly onto the needle. The other instruments are a sharp-pointed fine scalpel and a 10-millilitre "Record" syringe with needles for infiltration. At least ten millilitres of a 2% solution of "Novocain" are required. It is essential that all instruments should be kept as sharp as possible.

Technique of Puncture.

The technique is as follows.

1. The patient lies supine in bed with one pillow under the head and the right side of the body as near the edge of the bed as possible. The right arm is raised above the head or placed under the head.

2. The usual site for biopsy is the ninth or tenth intercostal space in the anterior or mid-axillary line. In obese people the latter site is obligatory.

3. The skin is infiltrated with 2% "Novocain" solution and then with a long fine needle the pleura is anæsthetized. Immediately after this the resistance of the diaphragm will be felt, and it is infiltrated widely to anæsthetize the peritoneum and finally the liver capsule. This is the most important step, and at least ten millilitres of "Novocain" solution will be required to ensure adequate anæsthesia.

4. At least three minutes by the clock should elapse to be certain of anæsthesia, and during this time the patient should practise holding the breath after several deep inspirations. It is absolutely essential for the breath to be held during biopsy, or tearing of the liver capsule may result.

5. A small preliminary skin incision is now made with the fine-pointed scalpel, and the biopsy needle is inserted at right angles to the skin. The patient is given the instruction "Hold your breath", and this should be done in mid-inspiration and not in full inspiration. The needle can be felt to penetrate the diaphragm and liver capsule. When it is inside the right lobe the trocar is withdrawn.

6. The liver specimen is now obtained by pushing the hollow needle further into the liver for another three centimetres. During the forward thrust it is rotated several times to ensure clear cutting of the specimen.

7. The "Luer Lok" syringe, containing four or five millilitres of normal saline solution, is now firmly attached and strong suction is maintained while the cannula is swiftly withdrawn. In order to have time, it is essential to have an assistant ready to hand one this syringe. When the cannula is withdrawn, the plug of liver tissue should be floating in the saline solution. Saline solution is preferred as a vehicle, as there is no danger if it is accidentally injected during the operation. Alcohol has the disadvantage of blocking the syringe when blood is aspirated.

8. In most cases some blood will be aspirated as well with the liver tissue, but this does not appear to be a cause for alarm. However, it is certainly disconcerting at first.

9. The wound in the skin is now sealed with collodion and the patient continues to lie still.

After-Care of the Patient.

With experience there should be no need for the routine use of morphine afterwards, as most patients do not feel any pain; but it should be used in all cases by those commencing to employ this technique. It is necessary if there is any evidence of hæmorrhage at the time, as revealed by shoulder tip pain immediately after biopsy. Strict bed rest should be enforced during the next twenty-four hours, and the pulse rate should be recorded each hour during this period. The patient should remain under observation for a further forty-eight hours before discharge from hospital is considered. In no circumstances is it permissible to carry out this procedure unless the patient is in hospital.

There may be some pain at the site of puncture during this period, but this is variable; it is uncommon for it to be severe. Two patients complained of pain on deep breathing, commencing twenty-four to forty-eight hours respectively after the biopsy and lasting for twenty-four hours.

Complications.

As was stated above, the greatest cause for anxiety is the risk of hæmorrhage; but with proper precautions this should be minimal. One patient (Case 16) who had been jaundiced for six months previously did show signs of intraperitoneal bleeding (pain, rigidity and some distension). Repeated examination of the blood failed to reveal any significant change in hæmoglobin value, and there was no evidence of any circulatory upset. In this instance there was an error in not giving morphine immediately symptoms became manifest. As a consequence the patient became restless, thereby aggravating the condition. Another patient (Case 13) submitted to laparotomy for obstructive jaundice twenty-four hours after biopsy was found to have two large blood clots in the subphrenic space. At no time had there been any complaint of pain or any alteration in pulse rate. On the other hand, two patients died from carcinomatosis within a week of biopsy, and at autopsy there was some difficulty in finding the site of puncture, and no evidence of hæmorrhage was found. Several other patients have undergone laparotomy after biopsy, and no sign of hæmorrhage has been found. Should serious hæmorrhage occur, the best treatment is a transfusion of fresh blood and injections of vitamin *K*.

Failures.

Even with a great deal of practice, there are occasions when one fails to obtain an adequate sample of liver tissue. This has happened on six occasions in this series, but the number decreases with growing experience. Two factors which play a large part are the presence of ascites and emphysema with a small liver. In ascites the abdominal cavity should be drained before biopsy is attempted, and in emphysema an attempt should be made to use as low a site as is compatible with safety. Well-developed cirrhosis makes the obtaining of a satisfactory specimen difficult owing to the toughness of the fibrous tissue. If the needle is kept sharp and rotated during insertion, this should be overcome.

Fixation of Tissue.

The plug of liver tissue is floated in saline solution into a kidney bowl, whence it is transferred with very fine forceps to the fixative. For routine work, Dr. J. W. Perry, pathologist to the Clinical Research Unit, and I have found Masson's solution most satisfactory, since it permits of routine staining (hæmatoxylin-eosin and Van Gieson's stain) as well as staining for glycogen. It is helpful to inspect the specimen, since in cirrhosis it is usually uneven and shaggy, while neoplastic tissue may appear paler than normal liver. It should be observed that there is quite a characteristic grating feeling on puncturing a cirrhotic liver.

Use of Aspiration Biopsy in Diagnosis and Prognosis.

Infective Hepatitis.

If biopsy is not undertaken at an early stage of infective hepatitis the typical picture of liver cell necrosis will not be seen; but in all the cases in this series there has been definite evidence of a preceding diffuse inflammation of the liver. This may be of real value in the making of the diagnosis, and also by giving useful evidence of the progress of the lesion. When the patient's clinical condition fails to improve satisfactorily, biopsy repeated after an interval gives information beyond the scope of biochemical tests as to the real state of the liver.

Obstructive Jaundice.

At times the cause of jaundice may be difficult to determine clinically. Aspiration biopsy in cases of mechanical obstruction to the bile duct will reveal a picture of accumulation of bile pigment in the central region without any damage to liver cells. It may also give useful information as to the presence of an unsuspected cholangitis. More important is the fact that it can usually save a patient with prolonged jaundice due to slowly resolving infective hepatitis from the risk of an exploratory laparotomy.

Cirrhosis of the Liver.

In cirrhosis of the liver biopsy can aid the clinician in assessing prognosis by illustrating the degree of severity of the condition as shown by the extent of disturbance of hepatic architecture and the degree of fibrosis. Aspiration biopsy has established the diagnosis of hæmochromatosis in two cases in which no glycosuria was present.

TABLE I.
Summary of Cases and Results.

Case Number.	Initials of Patient.	Clinical Diagnosis.	Biopsy Diagnosis.	Remarks.
1	B.H.	Carcinomatosis.	Secondary renal carcinoma.	Renal carcinoma with secondary deposits in the liver, confirmed by autopsy.
2	B.C.	Arsenotherapy jaundice.	Subsiding hepatitis.	
3	A.C.	Tertiary syphilis, hepatomegaly.	Non-specific mild hepatitis.	
4	N.S.[1]	Cirrhosis.	Cirrhosis.	
5	M.A.	Cirrhosis.	Cirrhosis.	
6	E.H.	Recurrent jaundice, possibly hepatitis.	Chronic hepatitis.	
7	E.N.	Possible Hodgkin's disease.	Secondary carcinoma of liver.	Small primary bronchogenic carcinoma. Extensive secondary deposits in mediastinum and liver found at autopsy.
8	A.N.	Obstructive jaundice, infective hepatitis.	Subsiding hepatitis.	
9	E.L.	Abdominal colic, hypertension.	Fatty infiltration of liver.	
10	P.C.[1]	Infective hepatitis.	Subacute hepatitis, commencing cirrhosis.	
11	C.L.	Diabetes, hepatomegaly.	Portal cirrhosis.	
12	R.E.	Chronic alcoholism.	Fatty liver, commencing cirrhosis.	
13	J.S.	Stone in common bile duct.	Obstructive jaundice.	No cause for mechanical obstruction found at laparotomy.
14	A.M.	Hæmochromatosis.	Hæmochromatosis.	
15	H.B.	Cirrhosis.	Cirrhosis.	
16	C.R.	Possible stricture of the common bile duct.	Obstructive jaundice.	
17	E.S.	Jaundice, possibly hepatitis.	Subsiding hepatitis.	
18	V.L.	Rheumatoid arthritis.	Normal liver.	
19	M.S.	Obstructive jaundice.	Secondary carcinoma of liver.	
20	G.M.	Hepatomegaly, possibly malignant disease.	Hepatoma.	
21	A.D.	Stone in common bile duct.	Obstructive jaundice.	Cholelithiasis with stones in common duct at operation.
22	S.	Splenomegaly, cause not known.	Normal liver.	
23	H.D.	Chronic gastric ulcer, nutritional deficiency.	Normal liver.	
24	E.McD.	Hepatomegaly.	Hæmochromatosis.	
25	W.D.	Obstructive jaundice.	Subsiding hepatitis.	
26	E.C.	Obstructive jaundice, possibly hepatitis.	Obstructive jaundice.	Carcinoma of common bile duct found at laparotomy.
27	G.J.	Rheumatic carditis.	Normal liver.	
28	J.G.	Macrocytic anæmia.	Normal liver.	
29	J.W.	Obstructive jaundice.	Obstructive jaundice, cholangitis.	Cholelithiasis with stones in common bile duct found at operation.
30	F.G.	Chronic hepatitis.	Multiple nodular hyperplasia.	
31	M.S.	Infective hepatitis.	Early nodular hyperplasia.	
32	J.N.	Obstructive jaundice.	Obstructive jaundice, cholangitis.	Cholelithiasis with stones in common duct at operation.
33	T.R.	Carcinoma of head of pancreas.	Obstructive jaundice, cholangitis.	Carcinoma of head of pancreas at laparotomy.
34	M.G.	Hepatomegaly.	Hæmochromatosis.	
35	S.M.	Pernicious anæmia.	Fatty infiltration of liver.	
36	W.G.	Possibly amœbiasis.	Cholangitis.	
37	W.R.	Alcoholism, dyspepsia.	Normal liver.	
38	A.G.	Infective hepatitis.	Multiple nodular hyperplasia.	
39	M.H.	Chronic hepatitis.	Chronic hepatitis, cirrhosis.	
40	L.R.	Jaundice.	Chronic hepatitis, cirrhosis.	
41	S.S.	Obstructive jaundice.	Obstructive jaundice, cholangitis.	Carcinoma of head of pancreas at laparotomy.
42	L.D.	Infective hepatitis.	Subsiding hepatitis.	
43	A.B.	Infective hepatitis, subacute atrophy.	Residual portal fibrosis.	
44	J.G.	Banti's syndrome.	Cirrhosis.	
45	A.S.	Alcoholism, hepatomegaly.	Fatty infiltration of liver.	
46	L.C.	*Diabetes mellitus*, cholangitis.	Fatty infiltration of liver, subsiding cholangitis.	Had undergone cholecystectomy for cholelithiasis and cholecystitis two weeks previously.
47	B.L.	Rheumatic fever.	Increased cellularity and fibrosis of liver.	
48	P.J.	Cirrhosis.	Chronic hepatitis.	

[1] Biopsy performed on two occasions at intervals of six months.

Carcinoma of the Liver.

Unless nodules can be felt and the transabdominal route used, biopsy cannot be said to exclude malignant disease of the liver when negative findings are obtained. In two cases, however, malignant disease was diagnosed by the use of the intercostal route.

Hepatomegaly.

In five cases of hepatomegaly a positive diagnosis has been possible only by the use of biopsy; two were cases of hæmochromatosis, one was found to be a case of hepatoma, one a case of cirrhosis and one a case of secondary carcinoma. It will be noted from Table I that in some cases normal liver was found.

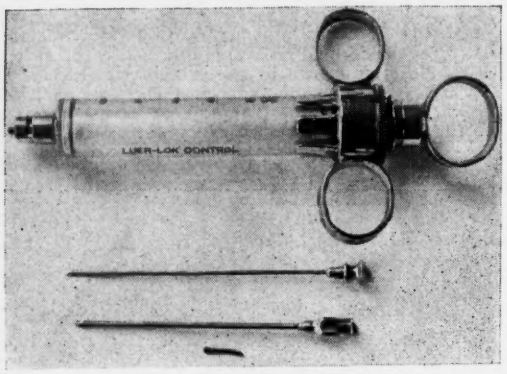

FIGURE VII.

Franseen needle with sharp-pointed trochar and hollow needle with serrated cutting edge on distal extremity. Also "Luer Lok" syringe and piece of liver column aspirated (2·5 centimetres).

Summary.

1. The technique of aspiration biopsy of the liver is described in detail, and the risks and difficulties of the procedure are discussed.

2. A series of fifty biopsies is analysed and the use of the procedure in diagnosis and prognosis is briefly discussed.

Acknowledgements.

I am deeply indebted to the honorary medical staffs of the Royal Melbourne Hospital, the Alfred Hospital and Saint Vincent's Hospital and to the medical staff at the 115th (Heidelberg) Military Hospital for making material available for the study. The photography in this paper has been done by Mr. E. Matthaei, of the University of Melbourne.

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(4) J. H. Dible, J. McMichael and S. P. V. Sherlock: "Pathology of Acute Hepatitis", *The Lancet*, Volume II, 1943, page 402.

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Appendix on Histological Technique.

(J.W.P.)

The specimen of liver obtained by aspiration biopsy is treated according to the principles laid down for routine histological tissue—namely, fixation, dehydration, clearing, embedding, sectioning, staining and mounting.

It is obvious that the extent of investigation of aspiration biopsy material is limited by the size of the specimen. Whilst it is desirable to examine as large an area of the available specimen as possible, it must be remembered that the choice of several stains often requires division of the specimen for treatment with different fixatives. It is wise therefore to consider each biopsy specimen as an individual problem in fixation and staining, as experience reveals that even the best of technical procedure produces occasionally a very small or fragmented piece, the division of which is either undesirable or impracticable.

In the present series the following staining methods were used when possible: (*a*) hæmatoxylin and eosin, (*b*) hæmatoxylin and Van Gieson, (*c*) Best's carmine, (*d*) Gomori's[1][2] method for alkaline phosphatase. The Prussian blue reaction for iron-containing pigment was occasionally used. Frozen sections are not usually permitted, because insufficient material is left on which to employ other staining methods.

Fixation.

If it is desired to stain the specimen for the presence of glycogen, one of the qualities of the fixative must be its low or absent water content. For such fixation Masson's fluid as recommended by Krarup[3] has been used. It has the following formula: trichloracetic acid 12 grammes, formalin (40%) 100 millilitres, saturated alcoholic solution of picric acid 20 millilitres, alcohol (93%) 400 millilitres. Krarup recommends fixation for twenty-four hours, followed by absolute alcohol, xylol and paraffin embedding. For aspiration biopsy material shorter fixation time is permissible, and the following scheme is suitable: (i) fixation in Masson's fluid, three to twelve hours; (ii) dehydration in absolute alcohol, three to twelve hours (usually one change of absolute alcohol); (iii) clearing in xylol, three to six hours; (iv) embedding in paraffin in a vacuum embedder for one hour (one change of paraffin). The above-mentioned scheme is empirical, and if certain principles are observed—namely, that prolonged exposure to strong alcohol, to most clearing agents and to heat makes tissue brittle—a scheme of one's own can be developed. Sometimes for convenience tissues are left for longer periods in fixative or subsequent fluids.

As Krarup indicates, and as has also been our experience, periods of twenty-four hours in Masson's fluid or in absolute alcohol are compatible with satisfactory sections. Masson's fluid is a suitable fixative for hæmatoxylin and eosin staining and also for hæmatoxylin, Van Gieson and Prussian blue staining.

For alkaline phosphatase Gomori[2] recommends fixation in 80% alcohol, and this has proved satisfactory. It is therefore necessary only to divide the specimen into two portions to employ all the stains mentioned above.

Dehydration.

Dehydration is performed in the usual way, by subjecting the specimen to absolute alcohol after fixation in Masson's fluid, and the same method is used after fixation in 80% alcohol as in Gomori's method for alkaline phosphatase.

Clearing.

Many clearing agents are satisfactory. Xylol was the one selected; it is a fairly rapid clearing agent. Gomori recommends benzene for alkaline phosphatase, and this has been used.

Embedding.

The advantage of vacuum embedding is that the time of exposure to heat is lessened by the more rapid permeation of the tissue. Its use is optional. It is, however, advisable to use new paraffin for embedding and blocking, and at least one change of paraffin whilst the specimen is in the embedder, especially if no vacuum is used.

Sectioning.

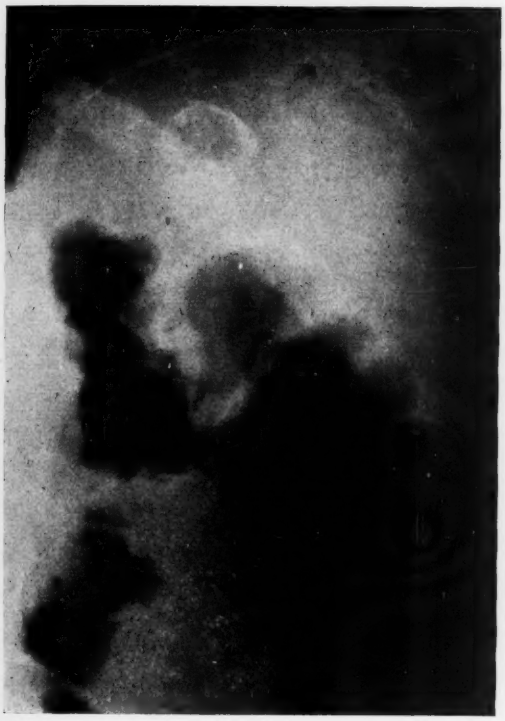
Sectioning was performed on a rocking microtome, the Cambridge Instrument Company's small model, and sections were cut with the instrument set at between 6μ and 7μ. They were cut parallel to the long axis of the cylindrical specimen, so that the longest available surface was obtained. A mixture of egg albumen and glycerin was used to fasten paraffin sections to glass slides.

Staining.

Particulars of the hæmatoxylin and eosin, hæmatoxylin and Van Gieson and Prussian blue reaction methods of staining can be obtained from any standard textbook; but it is thought desirable to describe Best's carmine method and the method for the detection of alkaline phosphatase activity.

Best's Carmine Method.—The usual procedure with this stain is to embed the specimen in celloidin or use celloidin protection films during aqueous staining. The use of

ILLUSTRATIONS TO THE ARTICLE BY DR. W. E. KING AND DR. J. W. PERRY.



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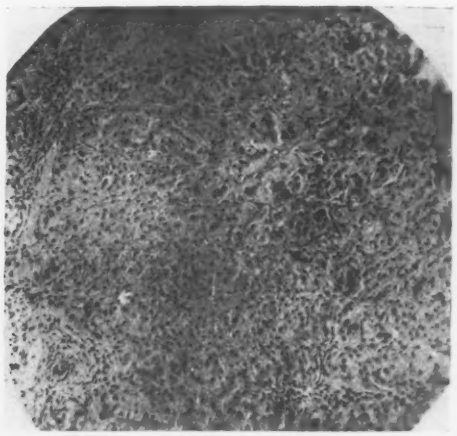

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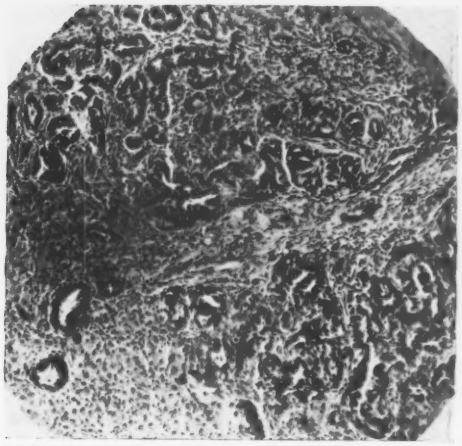

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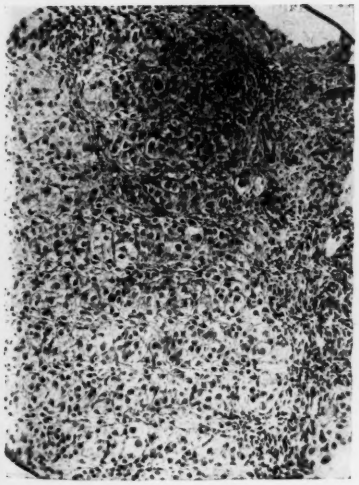

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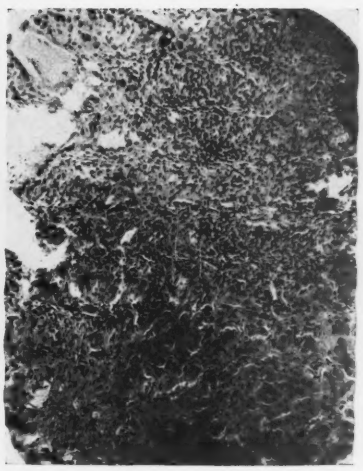

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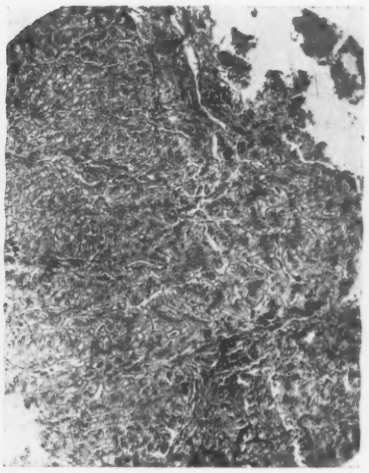

FIGURE VI.

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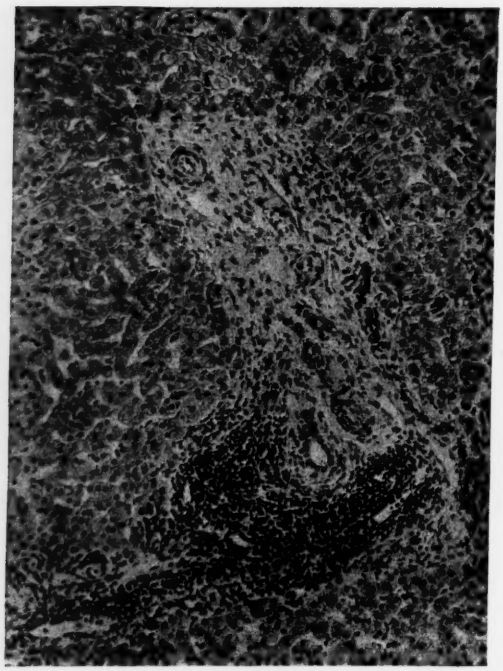

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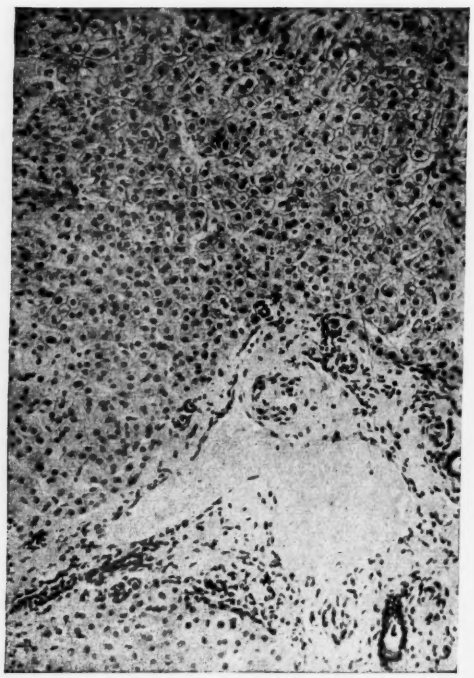

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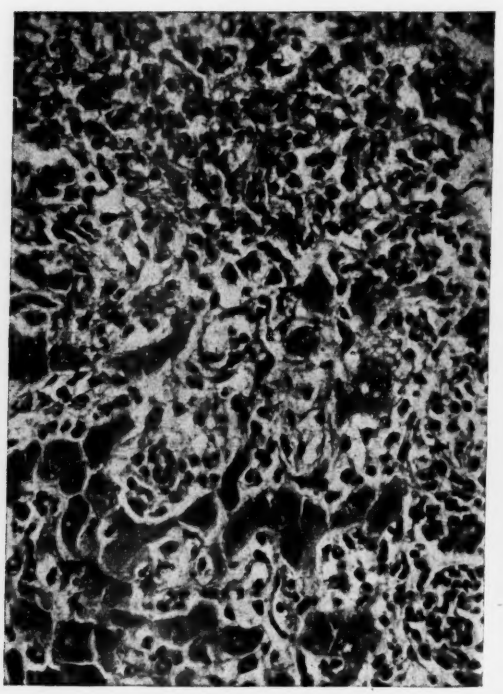

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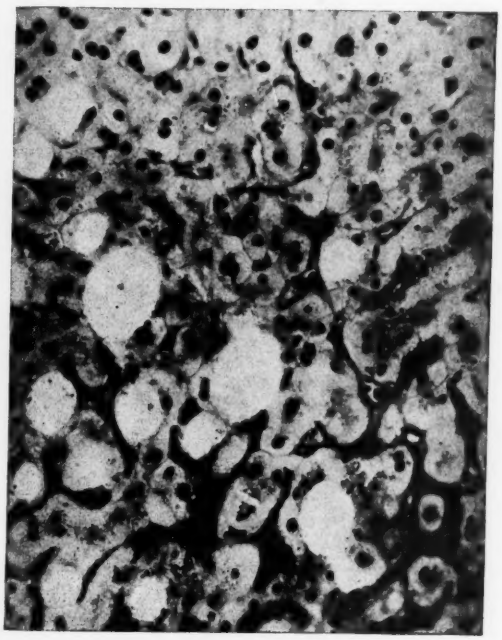

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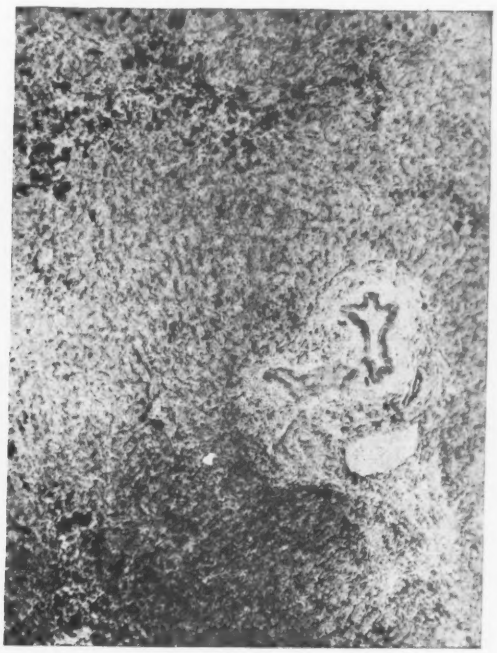

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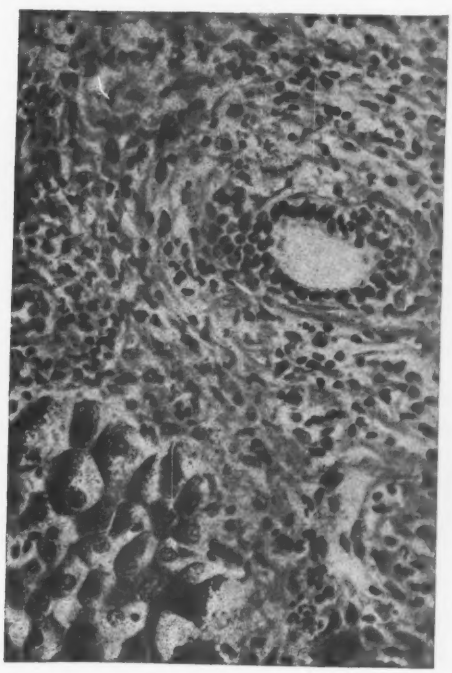

Figure VIII.

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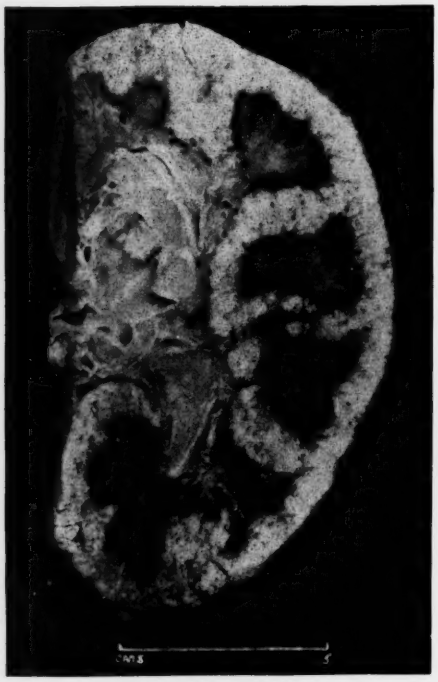

FIGURE I.

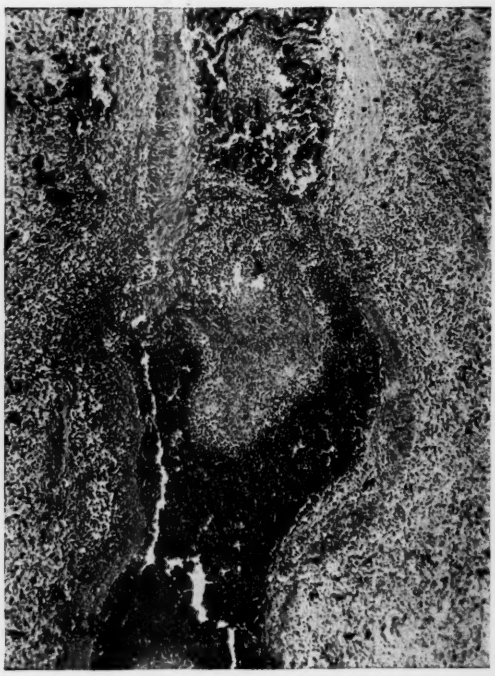

FIGURE II.

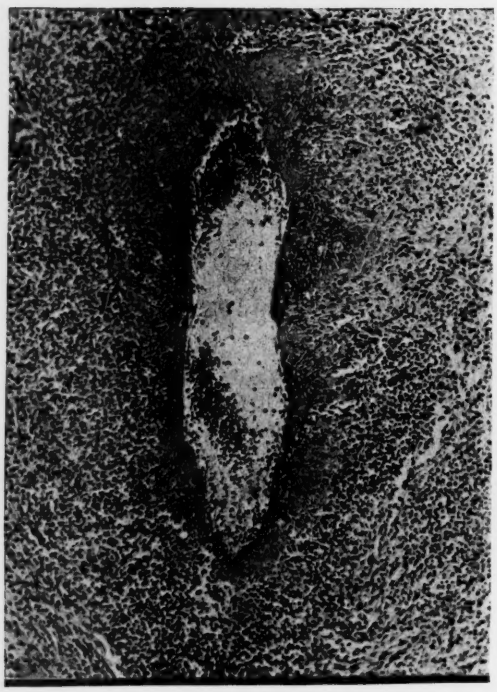

FIGURE III.

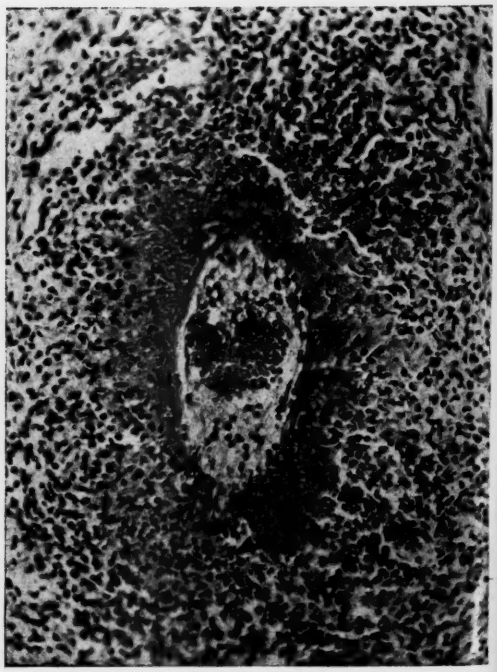

FIGURE IV.

Masson's fluid as a fixative dispenses with this, and the material may be treated as for ordinary sections. The method is set out as follows. Fix the specimen in Masson's fluid, dehydrate it in alcohol and clear it in xylol. Embed it and cut sections at 6μ or 7μ. Mount it on an albumenized slide from 70% alcohol warmed sufficiently to flatten the section. Water is avoided because it will dissolve the glycogen. The sections are then placed in an incubator at 37° C. overnight.

The rest of the method is as follows. (i) Remove the paraffin with xylol. (ii) Use absolute alcohol to remove the xylol. (iii) Transfer the specimen to Ehrlich's hæmatoxylin stain for ten to fifteen minutes. (iv) Rinse the specimen in 70% alcohol to remove the hæmatoxylin. (v) Transfer it to Best's carmine stain for five to ten minutes (see below). (vi) Differentiate it in Best's differentiating fluid (see below). (vii) Dehydrate it in absolute alcohol. (viii) Clear it in xylol. (ix) Mount it in neutral Canada balsam. Best's carmine stain stock solution consists of carmine two grammes, potassium carbonate one gramme, potassium chloride five grammes, and distilled water 60 millilitres. It is prepared as follows. Carefully boil the mixture for five minutes (this should be done in a flask of 200 millilitres' capacity on account of the frothing). Cool it and add 20 millilitres of concentrated ammonia. This solution must be kept in a tightly stoppered bottle in a dark, cool place—for choice in the refrigerator. It keeps for several weeks in summer and for two months (or longer) in winter. It should be filtered before use. The stain consists of the following constituents: Best's carmine stock solution two parts, concentrated ammonia two parts, methyl alcohol three parts.

Best's differentiating fluid consists of absolute methyl alcohol 40 millilitres, absolute ethyl alcohol 80 millilitres, and distilled water 100 millilitres.

Detection of Alkaline Phosphatase Activity.—After the specimen has been fixed in 80% alcohol for twelve to twenty-four hours and dehydrated with absolute alcohol, it is cleared in benzene. After it has been embedded in paraffin, sections are cut at 6μ or 7μ. After the removal of paraffin in xylol and the removal of xylol with absolute alcohol, the section is protected with a thin film of celloidin in the following manner: the slide is dipped into a 0·5% to 1·0% solution of celloidin in a mixture of two parts of ether and three parts of absolute alcohol, and then immersed in 90% alcohol for a few seconds to harden the celloidin. The slide is now dried in air or in the incubator at 37° C. This requires a short time only (ten to twenty minutes), and if necessary slides may be stored for future staining after this step. From here Gomori[2] recommends the following procedure: (i) Incubate the slides for one and a half hours at 37° C. in the following mixture: two or three parts of a 2% solution of sodium glycerophosphate and of a 2% solution of sodium barbital, one part of a 2% solution of calcium chloride or calcium nitrate, and five or six parts of distilled water. This mixture has a pH about 9·4. (ii) Rinse the sections thoroughly in a 0·5% to 1% solution of calcium chloride or calcium nitrate. (iii) Transfer the sections to a 2% solution of cobalt chloride or cobalt nitrate for two minutes. (iv) Rinse them thoroughly in repeated changes of distilled water. (v) Immerse them in a dilute solution of fresh light yellow ammonium sulphide (one millilitre to a Coplin jar) for one minute. (vi) Wash them under the tap for a few minutes. (vii) Counterstain them as desired. (viii) Dehydrate them, clear them and mount them in the usual way.

Difficulty in obtaining uniform counterstaining with dilute carbol fuchsin, eosin or methyl green has occasionally been experienced, and this was thought to be due to the presence of the celloidin film, which is not removed until the section comes in contact with a celloidin solvent during dehydration. It has been found that the removal of the film with equal parts of alcohol and ether after stage (ii) is consistent with satisfactory results and is followed by uniform counterstaining. Immersion in methyl green (1% aqueous solution) for one minute has been found most effective.

The presence of phosphatase activity is indicated by areas of black or brown sulphide deposit, which are easily seen against the contrasting background of a suitable counterstain. In sections showing a positive result it is necessary to exclude the possibility that the site of staining is conditioned by the presence of insoluble phosphates already in the tissue. This can be done by running through a second slide, omitting the substrate. If the result is still positive the reaction is not due to enzyme activity but to phosphates already present in the tissue. Further information regarding this technique can be obtained by consulting Gomori's papers.

Acknowledgements.

My thanks are due to my technician, Miss E. Davis, for her willing cooperation. Throughout this appendix, for the description of routine procedure, free reference has been made to "Histological Technique", Second Edition, 1938, by H. M. Carleton and G. A. Leach (Oxford University Press).

References.

(1) G. Gomori: "Microtechnical Demonstration of Phosphatase in Tissue Sections", *Proceedings of the Society of Experimental Biology and Medicine*, Volume XLII, 1939, page 23.
(2) G. Gomori: "Distribution of Phosphatase in Normal Organs and Tissues", *The Journal of Cellular and Comparative Physiology*, Volume XVII, 1941, page 17.
(3) N. B. Krarup: "Histological Examination of Glycogen, Especially in Hepatitis Epidemica", *Acta pathologica et microbiologica Scandinavica*, Volume XVI, 1939, page 402.

Legends to Illustrations.

FIGURE I.—X-ray film of liver area taken with patient in full expiration (Case 5), showing bowel adherent to the under-surface of the liver beneath the twelfth rib. The patient had previously undergone a cholecystectomy.

FIGURE II.—Case 26. Obstructive jaundice. There is a collection of bile pigment near the centre of the lobule, with only slight changes in the portal tracts.

FIGURE III.—Case 19. Obstructive jaundice. Secondary adenocarcinoma found at biopsy.

FIGURE IV.—Case 17. Subsiding hepatitis. Residual cellularity in the portal tracts and some hyperplasia of liver cells.

FIGURE V.—Case 30. Chronic hepatitis, nodular hyperplasia, showing regenerating liver tissue surrounded by zone of inflammatory fibrous tissue containing bile ducts, sinusoids and a few surviving liver cells.

FIGURE VI.—Case 34. Hæmochromatosis. Liver lobules separated by bands of fibrous tissue containing pigment. Note accumulation of pigment in liver cells.

SOME ASPECTS OF CHOLELITHIASIS AND OBSTRUCTIVE JAUNDICE.

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IT is the purpose of this paper to present some observations on 59 patients suffering from gall-stones or from tumours involving the biliary tract. The study has been primarily directed toward an evaluation of the associated hepatic changes by biochemical tests and where possible by the histological examination of biopsy specimens of the liver. It was hoped that in this way some explanation might be found for the well-known and often serious complications occurring in the post-operative period. The number of cases so far examined is insufficient to allow any definite conclusions to be made, but some interesting facts have been revealed which should guide future studies.

Because of the comprehensive physiological activity of the liver, it is desirable to use biochemical tests covering several of its different functions. From the large number available we have chosen those which for their respective purposes are simple to perform and provide useful information to the clinician.

The tremendous functional reserve of the liver[1][2] makes it necessary to accept all the results of all biochemical tests with caution.

Biochemical Methods.

The biochemical tests used in this series were chosen to cover different aspects of liver function. For the estimation of serum bilirubin content the quantitative Van den Bergh test was used, for bilirubin in urine Gmelin's test and for bile salts Hay's test. The hippuric acid excretion test was performed by the method of Quick,[3] the cephalin flocculation test by the method of Hangar,[4] alkaline phosphatase estimations by the method of King and Armstrong,[5] determination of the total serum

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protein content by the method of Phillips and Van Slyke,[6] and prothrombin estimations by the method of Quick, modified by Kark and Lozner.[7]

The Van den Bergh Reaction.

The qualitative Van den Bergh reaction can no longer be accepted as an indication of the underlying pathological process. This test is often misleading and the terms "direct" and "biphasic" serve only to describe a colour reaction when serum containing bile pigment is in contact with the diazo reagent of Ehrlich. The interpretation of the reaction in terms of the presence of direct and indirect reacting bilirubin has been challenged by Bockus,[8] Roberts,[9] Snider,[10] Corkhill *et alii*,[11] and it has been shown that even a strongly positive direct reaction does not necessarily indicate obstruction of the bile ducts outside the liver by a stone or tumour.

The quantitative test, however, serves two useful purposes. It enables jaundice to be detected before it is manifest at the bedside, and the course of a jaundiced patient's condition to be followed quantitatively by serial examinations. Levels above 1·0 milligramme per 100 millilitres of serum are considered to be abnormal. Although great variation occurs in abnormal serum bilirubin levels, patients with neoplastic obstruction tend to have higher readings than those with calculus obstruction.

Bile Components in Urine.

The presence of bilirubin in the urine follows fairly closely the serum levels. Careful examination of stools macroscopically is of definite value, as often with a falling serum bilirubin level normal colour returns to the fæces. The colour of the stools is therefore a most useful guide to the degree of obstruction.

The Hippuric Acid Excretion Test.

In this series the oral method has been used for the hippuric acid excretion test, but difficulties have been encountered with ill patients owing to nausea and vomiting. For this reason the intravenous method has recently been adopted for selected cases. The test is a valuable index of liver function, but fails to detect slight damage. In the present series those patients with biliary obstruction show a tendency to lowering of the total excretion of benzoic acid. The test is of no value in differentiating the more common causes of jaundice, such as gall-stones, tumour and infectious hepatitis. Repeated estimations are of value in prognosis. However, an impaired excretion does not *per se* provide an absolute contraindication to operation. A good review of this test is given by Rennie.[12]

The Cephalin Flocculation Test.

The cephalin flocculation test is one of a number of serological tests including the colloidal gold, Takata-Ara and thymol turbidity tests. These depend on the alteration of a physical state which can be observed, such as colour in colloidal gold tests and flocculation in Hangar's test. The exact mechanism of these reactions is not clear, but they depend on the relative levels of serum proteins (Kabat *et alii*[13]).

The positive results in some infections, particularly in infectious hepatitis, may be due to the rise in serum globulin content coincident with the rise in the level of antibodies in the blood stream. Though not in fact a test of liver function, the result of the cephalin flocculation test is often positive in diseases involving the liver and especially in infectious hepatitis. If a strongly positive reaction is obtained in a case of jaundice of short duration then it is likely that the jaundice is due to infectious hepatitis. Sometimes in this disease only a weak positive reaction occurs (Wood *et alii*[14]). Moreover, a strongly positive reaction in the cephalin flocculation test may be found in other diseases, notably in other virus infections such as acute mononucleosis and in chronic alcoholic hepatitis.

In the present series, in cases of jaundice due to obstruction, usually a negative result was obtained. In the few cases in which there was a positive result (which was, however, usually only "one plus") there was found either considerable cholangitis or involvement with secondary carcinoma.

Alkaline Phosphatase.

Sharnoff *et alii*[15] state that in the absence of skeletal disease alkaline phosphatase levels depend initially on the degree of damage to liver cells. It is controversial why phosphatase levels are raised in liver disease. Wachstein and Zak[16] maintain that alkaline phosphatase levels are not reliable in differentiating obstructive from non-obstructive jaundice. Roberts[9] states that in gross obstructive jaundice due to calculus or to a pancreatic carcinoma the blood phosphatase level is invariably high, whereas in all other varieties of jaundice the level is but slightly raised and may even be normal. Our findings show that variable results are to be expected, but mechanical obstruction is usually associated with higher levels than infectious hepatitis. There are various theories to explain this rise in alkaline phosphatase level. Bullard[17] claims that in biliary obstruction not only is the liver unable to excrete phosphatase, but the bile phosphatase is produced locally in greater quantities. This hypothesis is not proven, but this does not detract from the value of a test which is helpful when used in conjunction with other liver tests.

Prothrombin Index.

It is usual to administer vitamin *K* to jaundiced patients undergoing operation. This serves to ensure a high prothrombin level. In the cases which do not respond, a blood transfusion is indicated. Low levels have rarely been encountered in our limited series. Fantl[30] claims that a tendency to hæmorrhage does not occur until the prothrombin index falls below 50%. All our patients with jaundice who have come to operation have been given vitamin *K* parenterally and no serious post-operative hæmorrhages have occurred.

Fractional Test Meal.

Most of the patients in our series with gall-stones had a low level or absence of free hydrochloric acid in the stomach following a gruel meal. The numbers are insufficient to be statistically significant. In seven of the cases of a low level or absence of free hydrochloric acid a test meal repeated between three and six months after operation showed no significant change.

Microscopic Examination.

Materials and Methods.

In this series the histological study was made mainly on biopsy material obtained either by aspiration or at operation. In all fatal cases autopsy material was obtained. The technique of aspiration biopsy used has been recently described by King and Perry.[18] In the operation biopsies a small wedge of liver one centimetre in depth was excised from the inferior margin of the left or right lobe. The site was closed with mattress sutures. No complications have arisen. Two patients upon whom biopsy was performed as above subsequently died of secondary malignancy and the site of incision was examined. In both instances the process of repair was well established with a minimum of local change.

Histological Methods.

Staining with routine hæmatoxylin and eosin and a connective tissue stain was performed on all material. In addition, examinations for glycogen, alkaline phosphatase and fat were made.

For staining fat the frozen section technique was adopted after fixation in 4% formol saline. Sudan (iv) was used for the staining. For glycogen Masson's fixative was used as used by Krarup,[19] followed by Best's carmine or Feulgen Bauer method. The advantage of Masson's fixative is that its use dispenses with the tedious methods involving the use of celloidin imbedding or celloidin protection films. This method produces good results and they are easily obtained.

For alkaline phosphatase Gomori's[20] method was used after fixation in 80% alcohol. By trial it was found that: (*a*) frozen formol-fixed tissue gave satisfactory results if after thawing it was dehydrated in the usual way and stained with routine hæmatoxylin and eosin or Van Gieson stain; (*b*) Masson's fixative can be used satisfactorily for hæmatoxylin and eosin and Van Gieson stains as well as for glycogen.

The interpretation of biopsy specimens from the liver requires careful consideration of a number of factors. Since such specimens necessarily involve immediately subcapsular portions of the liver substance, a knowledge of the normal variation in capsule thickness and of the character of liver cell architecture in this region is necessary. Any increase in thickness is usually due to the presence of moderately acellular collagen. Moreover, a thin zone of liver immediately below the capsule, several cells in depth, may show changes not depicted in deeper zones, the intercellular connective tissue being increased and continuous with the connective tissue of the capsule.

In spite of these differences from the structure of the deeper liver substance, however, it is considered that the subcapsular zone provides useful information concerning the histological structure of the liver.

The Pathology of the Liver in Cholecystitis.

Graham's[21] work on biopsy specimens removed at operation from the right lobe of the liver suggested that in inflammatory conditions of the gall-bladder there was always involvement of the liver. With acute and subacute infection of the gall-bladder the liver changes consisted in leucocytic infiltration in the portal canals commensurate with the intensity of the condition in the gall-bladder. In chronic cholecystitis there was often a picture identical with "an early case of cirrhosis".

Peterman, Priest and Graham[22] showed that in dogs with experimentally produced cholecystitis, changes could

TABLE I.

Patients with Gall-Stones without Previous History of Jaundice.

Case Number.	Age. (Years.)	Sex.	Duration of Symptoms.	Maximum Free Hydrochloric Acid.	Abnormal Biochemical Tests.	Liver Biopsy.
1 J.W.	31	F.	Two months.	5°	Alkaline phosphatase level, 35 units.	
2 R.W.	43	F.	Nine years.	4°	Nil.	Left lobe normal.
3 N.S.	43	F.	Three years.	5°	Nil.	
4 D.P.	36	F.	Two years.	12°	Cephalin flocculation: ++ (24 hours). +++ (48 hours).	
5 R.G.	49	M.	Three months.	12°	Nil.	Left lobe normal.
6 L.M.	42	F.	Two and a half months.	Nil	Nil.	Right lobe gall-bladder fossa region: fibrosis and round cell infiltration of portal tracts.
7 D.H.	24	F.	Seven weeks.	20°	Hippuric acid 1·8 grammes (2·2 grammes later).	Left lobe normal.
8 L.N.	31	F.	Twelve months.	12°	Nil.	
9 K.K.	50	F.	Three years.	40°	Nil.	Left lobe normal.
10 M.B.	60	F.	Twelve months.	Nil	Cephalin flocculation: +++ (24 hours). ++++ (48 hours).	Right lobe near gall-bladder: early biliary cirrhosis.
11 A.B.	44	F.	Twelve months.	20°	Nil.	Left lobe normal.
12 J.H.	31	F.	Nine months.	8°	Nil.	
13 E.I.	26	F.	Two years.	10°	Nil.	Left lobe normal.
14 R.W.	55	F.	Five weeks.	9°	Nil.	Right lobe gall-bladder fossa region: increase in portal connective tissue and round cell infiltration.
15 L.C.	62	F.	Four days.	38°	Nil.	Fatty infiltration. Patient a diabetic. Treated for two years.
16 B.W.	42	F.	Five years.	5°	Nil.	Left lobe normal.
17 M.R.	33	F.	Four years.	10°	Nil.	Left lobe normal.
18 J.B.	36	F.	Eighteen months.	20°	Nil.	Left lobe normal.
19 E.B.	51	M.	Ten years.	*Achylia gastrica.*	Nil.	Right lobe: portal tract fibrosis and round cell infiltration.
20 E.P.	50	F.	Twelve months.	Nil	Nil.	Left lobe: normal. Right lobe: fibrosis and round cell infiltration of portal tracts. (See Figures I and II.)
21 E.W.	58	F.	Five months.	44°	Nil.	
22 E.M.	66	F.	Two months.	23°	Nil.	

be observed similar to those seen in man, but that the right lobe was affected far more than the left and the most pronounced changes were in the right lobe adjacent to the gall-bladder. This fact supported their hypothesis that infection of the gall-bladder involved adjacent liver by way of lymphatics.

Judd[23] supported the views of Graham regarding the invariable involvement of the liver in cholecystitis, whilst Martin[24] at a later date, agreeing with Graham that cholecystitis is frequently the forerunner of hepatitis, drew attention to the fact that the hepatitis is rarely of clinical importance and is never progressive after the removal of the gall-bladder. This observation supports the contention that this localized hepatitis is caused and maintained by the diseased gall-bladder and does not support one of Graham's original contentions that gall-bladder inflammation is frequently secondary to hepatitis. And finally Wilkie[25] showed that experimentally produced cholecystitis in rabbits leads to involvement of the liver, whereas if previously to the production of cholecystitis the gall-bladder was separated from the liver and greater omentum interposed no involvement of the liver occurred.

Thus the accumulated evidence of most workers has indicated that hepatitis which is associated with acute cholecystitis and not accompanied by obstruction to the common bile duct is due to direct spread of infection from the gall-bladder into the liver. Our findings agree with this conception for we have found that the involvement of the liver is localized and the intensity varies inversely with the distance from the gall-bladder fossa.

The 59 cases in the present series have been divided into three groups. In the first group are included cases of gall-stones with no associated history of jaundice, representing uncomplicated cholelithiasis in which it was considered that the disease of the biliary tract was most probably confined to the gall-bladder. The second group comprises cases of gall-stones with jaundice or a definite history of jaundice, representing cholelithiasis with obstruction to the common bile duct. Here it was reasonable to presume that abnormal biochemical findings together with histological changes were most likely to be found. The cases of carcinoma form the third group.

Group I: Gall-Stones without Previous History of Jaundice.

In the present series there were twenty-two cases in this group, in only four of which abnormal results were obtained from liver function tests (see Table I). Serum alkaline phosphatase levels were estimated in only ten of the cases. The occurrence of solitary abnormal results in a group of routine liver function tests is difficult to explain and there was no evidence that these had any influence on the operative risk or the subsequent course. In twenty of the cases in this group the stones were confined to the gall-bladder. In the remaining two there were small stones in the common bile duct in spite of the absence of a history of jaundice. The biochemical tests and liver biopsy findings were normal in these two cases. The following are the four cases with abnormal biochemical tests:

CASE 1.—J.W., a female, aged thirty-one years, suffered from recurrent attacks of biliary colic for two months. Plain X-ray pictures showed opaque calculi. A cholecystectomy was performed. The gall-bladder contained stones. No stones were palpated in the common bile duct, which appeared normal. The liver was normal macroscopically. No biopsy was obtained. On microscopic examination the gall-bladder was the site of chronic inflammation. The only indication of abnormal liver function was an alkaline phosphatase level of 35 units. Convalesence was satisfactory.

CASE 4.—D.P., a female, aged thirty-six years, suffered from attacks of classical biliary colic for two years. X-ray examination showed calculi and a non-functioning gall-bladder. Cholecystectomy was performed. The gall-bladder contained stones, but palpation of the common bile duct, which appeared normal, failed to reveal any stones. The liver was normal macroscopically. No biopsy was obtained. On microscopic examination the gall-bladder was found to be the site of chronic inflammation. The only abnormal result of a biochemical test was a weak positive cephalin flocculation which returned to normal after operation. The post-operative course was satisfactory.

CASE 7.—D.H., a female, aged twenty-four years, suffered from attacks of pain over the gall-bladder for seven weeks with occasional attacks of colic. Cholecystography showed several calculi. Cholecystectomy was performed. There were stones in the gall-bladder, but no stones could be palpated in the common bile duct which appeared normal. The liver was normal macroscopically. A biopsy specimen from the left lobe was normal. The gall-bladder showed chronic inflammatory changes. Hippuric acid excretion was 1·8 grammes. Convalescence was satisfactory. Three months later the hippuric acid excretion had risen to 2·2 grammes.

CASE 10.—M.B., a female, aged sixty years, suffered from pain in the region of the gall-bladder with intermittent colic for twelve months. Plain X-ray films showed calculi. Cholecystectomy was performed. The gall-bladder contained stones, but no stones were palpated in the common bile duct which appeared normal. The liver was normal macroscopically. A biopsy specimen was obtained from the right lobe approximately one inch from the gall-bladder fossa. It showed disturbance of normal architecture and fat accumulation in liver cells. The connective tissue of the portal tracts was increased and infiltrated with round cells. Bile duct hyperplasia was present. The picture was one of an early biliary cirrhosis and the changes could be attributed to the proximity of the gall-bladder. There was a strongly positive result from the cephalin flocculation test which became less strongly positive three months after operation. The convalescence was satisfactory.

Of the twenty-two cases in this group, fifteen have been studied with the aid of biopsy material. Ten biopsy specimens were obtained from the left lobe lateral to the falciform ligament and four biopsy specimens were obtained from the right lobe close to the gall-bladder fossa. In one case specimens were obtained from both the left and right lobes. The total biopsy specimens studied in this group is therefore 16 specimens from 15 patients. Of the four specimens obtained from the right lobe only, one has already been described (Case 10) which showed advanced chronic inflammatory changes resembling biliary cirrhosis. The remaining three showed evidence of chronic inflammation in the portal tracts. In Case 20, in which specimens from both lobes were obtained, the specimen from the left lobe was within normal limits and there was evidence of old inflammation in the portal tracts of the right lobe. Figures I and II illustrate this finding. In this group all the specimens taken from the left lobe of the liver showed a normal microscopic picture. Occasional slight increase of intercellular connective tissue or slight fat accumulation was considered to be attributable to the age and obesity of the patient.

Group II: Gall-Stones with Jaundice or with a History of Jaundice.

There were twenty-three cases in this group, all of the patients being subjected to biochemical investigation and laparotomy. In eighteen cases biopsy material was obtained. Sixteen patients were admitted to hospital with obstructive jaundice, the remaining seven gave a definite history of jaundice. The jaundiced patients usually showed progressive diminution of jaundice and in most cases operation could be delayed until the serum bilirubin content approximated normal. Material has therefore been available from patients showing obstructive jaundice and from some with no present evidence of obstruction but a definite history of jaundice in the past. Those patients in whom significant histological changes were found in the liver were either jaundiced at the time the biopsy was performed or had been jaundiced within the immediate past weeks. The histological changes were greatest in the portal tracts and consisted of increased cellularity including polymorphonuclear leucocytes. The portal connective tissue showed an increase and an openwork appearance suggestive of œdema. The bile ducts showed changes both in the epithelium and in the wall. In the epithelium all changes were seen from swelling and loss of cell outline in the early stages to polymorphonuclear infiltration (see Figures III and IV) and desquamation of epithelium. In some cases of long-standing obstruction proliferation of bile duct elements occurred, either as an increase in

TABLE II.
Patients with Gall-Stones Admitted with Jaundice or with History of Jaundice.

TABLE II.

Patients with Gall-Stones Admitted with Jaundice or with History of Jaundice.

Case Number.	Age. (Years.)	Sex.	Duration of Symptoms.	Hippuric Acid Excretion. (Normal: Three or more Grammes.)	Test Meal: Maximum Free Acid. (Normal: 60°.)	Urine Bile. (Normal: Nil.)	Serum Bilirubin Level. (Normal: 0·2 to 2·0 Unit.)	Cephalin Flocculation. (Normal: Nil.)	Serum Alkaline Phosphatase Level. (Normal: 3·0 to 13·0 Units.)	Serum Protein Content. (Normal: 6·0 to 8·5 Grammes *per Centum*.)	Prothrombin Index. (Normal: over 80%.)	Remarks.
23 H.F.	78	M.	1 week.	1·66	Nil	+	5	Nil	44	5·9	105	—
24 J.N.	62	M.	2 months.	1·11	15	++	10	Nil	12	6·3	94	Aspiration biopsy: moderately severe cholangitis.
25 A.H.	65	F.	9 months.	1·2		+	24	Nil	72	7·3		Acute pancreatitis and suppurative cholangitis found *post mortem*.
26 A.D.	53	M.	4 days.	3·0	25	++	16	Nil	30	7·2	80	Aspiration biopsy: mild cholangitis and increased alkaline phosphatase. Operation biopsy left lobe: recovery occurring. Alkaline phosphatase not increased.
27 J.W.	66	M.	12 months.	2·0		++	6	++ (48 hours)	28	5·4	90	No cephalin flocculation three weeks later. Aspiration biopsy: early cholangitis. Operation biopsy: recovery.
28 B.B.	60	F.	3 months.		Nil	Nil	1	Nil		6·8	96	Operation biopsy right lobe adjacent to gall-bladder: periportal fibrosis.
29 M.L.	65	F.	12 months.	1·92	60	++	10	Nil	20	5·9	105	Right lobe operation biopsy: cholangitis and portal fibrosis.
30 I.B.	50	F.	3 weeks.	1·83	Nil	++	15	Nil	52	6·1	100	—
31 E.L.	27	F.	9 months.	1·47	Nil	+++	40	Nil	35	6·3	100	—
32 M.R.	61	F.	4 months.	3·0	2	+	6	Nil	58	6·1		Left lobe operation biopsy: early cholangitis.
33 J.S.	63	M.	4½ months.			+	30	+ (24 hours) +++ (48 hours)	32	6·1	94	Biliary cirrhosis and cholangitis *post mortem*.
34 N.B.	29	F.	7 months.		34	+	0·5	Nil	27	6·5	102	Operation biopsy right lobe: cholangitis, periportal fibrosis.
35 E.W.	32	F.	5 months.	3·6	18	Nil	0·4	Nil		7·0		Operation biopsy left lobe: liver within normal limits.
36 C.P.	63	M.	12 months.	1·4 (150 cubic centimetres) 2·85	Nil Nil	+ Nil	2·5 0·4	Nil Nil	23 10·5	6·8	100	Operation biopsy right lobe: periportal fibrosis, bile duct proliferation, round cell infiltration.
37 E.B.	34	F.	6 years.	3·34	Nil	Nil	0·1	Nil		6·7		Operation biopsy right lobe: periportal fibrosis, bile duct proliferation, round cell infiltration.
38 A.B.	56	F.	6 years.	4·0	8	Nil	0·2	Nil		6·25		Operation biopsy right lobe: periportal fibrosis, bile duct proliferation, round cell infiltration.
39 B.B.	44	F.	4 months.	2·03	26	Nil	0·2	Nil	8	6·5	97	—
40 L.H.	22	F.	4 months.	2·58	15	Nil	0·2	Nil	7	7·0	100	Operation biopsy left lobe: mild cholangitis.
41 E.G.	71	F.	5 months.	1·63	15	+	2	+ (24 hours)	69	6·7	146	Operation biopsy left lobe: mild cholangitis.
42 A.P.	51	F.	2 years.	1·4	32	+	4	Nil	46	7·0	112	—
43 J.C.	43	F.	6 years.				0·2	Nil	12·5	6·5	89	Operation biopsy right lobe: evidence of old fibrosis with mild cholangitis superimposed.
44 J.N.	66	F.	2 years.	1·83	Nil	Nil	0·2	Nil	20·5	6·8		—
45 W.F.	53	M.	10 weeks.	1·4		Nil	1	Nil	14	6·8	100	—

TABLE III.

Patients with Jaundice Due to Neoplastic Obstruction.

Case Number.	Age. (Years.)	Sex.	Duration of Symptoms.	Hippuric Acid Excretion. (Normal: Three or more Grammes.)	Test Meal: Maximum Free Acid. (Normal: 60°.)	Urine Bile. (Normal: Nil.)	Serum Bilirubin Level. (Normal: 0·2 to 2·0 Unit.)	Cephalin Flocculation. (Normal: Nil.)	Serum Alkaline Phosphatase Level. (Normal: 3·0 to 13·0 Units.)	Serum Protein Content. (Normal: 6·0 to 8·5 Grammes *per Centum*.)	Prothrombin Index. (Normal: over 80%.)	Remarks.
46 M.S.	67	F.	12 weeks. Jaundice.		23	+++	37 25	Nil Nil	68	5·4	97	Aspiration biopsy: secondary carcinoma of liver and mild cholangitis; alkaline phosphatase increased.
47 E.C.	49	M.	6 months.	3·12	27	+++	30 43 40	++ (24 hours) +++ (48 hours) Nil Nil	31	6·7	100	Aspiration biopsy: early suppurative cholangitis.
48 W.S.	56	M.	6 weeks.	2·2	10	+++	33 20 43	Nil Nil Nil	53	5·4	82	Operation biopsy: early suppurative cholangitis.
49 S.H.	83	M.	3 weeks.		Nil	+++	40	Nil	8	5·75	83	Post-mortem findings: carcinoma of pancreas and biliary cirrhosis.
50 V.H.	37	F.	1 month.	0·38	10	++	20	Nil	50	5·75	88	Post-mortem findings: carcinoma of stomach and biliary cirrhosis.
51 H.Z.	78	F.	1 year.	0·98		++	33 40	Nil Nil	76·5	5·7		Aspiration biopsy: early biliary cirrhosis.
52 H.C.	66	M.	2 weeks.			++	25	++ (24 hours) +++ (48 hours)	54	5·2	70	Post-mortem findings: carcinoma of gall-bladder and extensive secondary hepatic deposits.
53 T.R.	46	M.	6 weeks.	2·89	45	+++	15 20	Nil Nil	62	6·5	100	Aspiration biopsy: early suppurative cholangitis.
54 S.C.	80	F.	6 weeks.			++	20	+ (24 hours) ++ (48 hours)	40	5·2	46	Post-mortem findings: suppurative cholangitis and biliary cirrhosis.
55 P.M.	55	M.	3 months.	2·28	27	+++	10	Nil	19	5·7	100	Aspiration biopsy: mild cholangitis.
56 S.S.	42	M.	2 months.	2·8	47	+++	20	Trace (24 hours) ++ (48 hours)	67	7·0	82	Operation biopsy: suppurative cholangitis; alkaline phosphatase increased.
57 G.R.	59	M.	3½ months.	2·54		+++	20	Nil	58	6·8	86	Operation biopsy: mild cholangitis and early biliary cirrhosis.
58 P.P.	56	M.	10 months.	2·9		+++	20	Nil	92	4·3	100	Aspiration biopsy: mild cholangitis.
59 L.M.	70	M.	2 months.	2·3	47	+	7	Nil	26	4·3	79	Operation biopsy: mild cholangitis and biliary cirrhosis; alkaline phosphatase not increased.

thickness of the epithelium or as an increase in the number of small ducts.

Whilst the changes were greatest in the portal tracts, the surrounding liver lobules were invaded by outward extensions of connective tissue and inflammatory cells. Retention of bile pigment was frequently seen in the central lobular areas where it occurred as aggregates in liver cells or canaliculi.

These changes represent the early stages of biliary cirrhosis, but in our experience they are reversible should the obstruction be relieved. However, without relief of obstruction, florid biliary cirrhosis develops, provided its progress is not interrupted by the occurrence of fatal cholangitis with abscess formation.

Examination of biopsy material has demonstrated that in cases of obstructive jaundice inflammatory changes in the portal tracts are present early in the disease. The presence of cholangitis, as shown by damage to bile ducts and polymorphonuclear infiltration, may be seen when clinically there is little evidence of infection. The clinical condition of "Charcot's intermittent hepatic fever" represents an advanced and uncommonly reached stage. The gravity and significance of Charcot's intermittent hepatic fever have been discussed by Hailes.[26]

When obstruction to the common bile duct was not a feature of the immediate past, the liver showed a range of changes varying from residual fibrosis in the portal tracts to normal. The relative parts played by bacterial and chemical factors in the development of these changes in the portal tracts has yet to be decided, though it would seem that the bacterial element is important in cases where suppuration is prominent.[27][28][29]

The following three cases are typical of this group. All the patients suffered from jaundice and stones were removed from the common bile duct. Biopsy studies revealed cholangitis of varying severity.

CASE 27.—J.W., a male, aged sixty-six years, suffered from right upper abdominal pain for twelve months. Forty-eight hours prior to admission to hospital he had an attack of colic followed by rigors, pyrexia and jaundice. The stools were pale in colour, the urine was dark. Examination showed tenderness and rigidity on the right side in the upper part of the abdomen. The patient ran a swinging temperature and the jaundice persisted for eight days. Biochemical tests showed the serum bilirubin content elevated (six units), bile salts and pigments were present in the urine, hippuric acid excretion was impaired (two grammes), the serum alkaline phosphatase level was raised (28 units), the serum proteins were normal and the cephalin flocculation test yielded a negative result. An aspiration biopsy specimen taken four days after the onset of jaundice showed cellular infiltration of the portal canals and polymorphonuclear leucocytes were present between the liver cells some distance away. (See Figures III and IV.) The appearance was that of early cholangitis. Section of the liver showed the presence of increased alkaline phosphatase. Twenty days after the aspiration biopsy cholecystectomy was performed. The common bile duct was opened, but no stones were found. The gall-bladder was chronically inflamed and there was a fistula between Hartmann's pouch and the common bile duct, apparently due to a stone's having ulcerated through. A liver biopsy specimen taken from the left lobe revealed considerable improvement in relation to the cholangitis, but a few polymorphonuclear leucocytes were still present amongst the liver cells. There was variation in size and shape of the liver cells and occasional mitotic figures were present. The appearance was that of subsiding cholangitis which had been accompanied by some degree of hepatitis. Convalescence was uneventful.

CASE 26.—A.D., a male, aged fifty-three years, had several attacks of biliary colic over a period of fourteen years, but no history of jaundice until his last attack four days before admission to hospital. On admission he was jaundiced with tenderness and rigidity on the right side in the upper part of the abdomen. The liver was palpable. There was no pyrexia. Biochemical tests showed that the serum bilirubin content was elevated (16 units), bile salts and pigments were present in the urine, hippuric acid excretion was not impaired, the serum alkaline phosphatase level was raised (30 units), serum proteins were normal and the result of the cephalin flocculation test was negative. The jaundice subsided, and aspiration biopsy carried out ten days after the onset of jaundice showed mild polymorphonuclear infiltration in the connective tissue of the small portal tracts. The liver cells showed slight fat accumulation. The diagnosis was mild cholangitis. Three days later cholecystectomy was performed and stones were removed from the common bile duct. A biopsy specimen obtained from the left lobe showed changes similar to the aspiration biopsy specimen, but there was more bile pigment retention in liver cells and bile canaliculi. There was histological evidence of increased alkaline phosphatase (Figure V).

CASE 24.—J.N., a male, aged sixty-two years, had a left hemiplegia for five years following a cerebral thrombosis. For two months he suffered from pain in the epigastrium and in the upper part of the abdomen on the right side, and he became jaundiced three days before admission to hospital. There had been no colic or rigors. Examination revealed slight jaundice. The liver was not palpable and there was neither rigidity nor tenderness. Biochemical tests showed that the serum bilirubin level was raised (10 units), bile salts and pigments were present in the urine, hippuric acid excretion was impaired (1·1 grammes), the serum alkaline phosphatase level was normal (12 units), the serum proteins were normal and the result of the cephalin flocculation test was negative. A plain X-ray film showed no opaque calculi. A cholecystectomy was performed and several calculi were removed from the common bile duct. The gall-bladder contained seven mulberry calculi and on microscopic examination revealed chronic inflammatory changes. An aspiration biopsy taken thirteen days after the onset of jaundice showed a mild cholangitis. Polymorphonuclear leucocytes were present in the periportal connective tissue and some between the liver cells. At operation seven days later a specimen of liver removed from the left lobe showed little alteration. A section showed an increase in alkaline phosphatase. After operation the patient's condition deteriorated. His temperature was elevated and hiccups were persistent. He developed bronchopneumonia and died after nine days. At post-mortem examination there was coronary sclerosis with myocardial scarring and extensive bronchopneumonia. There was an acute pancreatitis, with hæmorrhage and limited fat necrosis. The pancreatic and common bile ducts were both clear. The liver was enlarged (2050 grammes) and on section showed cholangitis and early biliary cirrhosis.

Group III: Jaundice due to Extrahepatic Obstruction by Neoplasm.

The third group, jaundice due to external obstruction by neoplasm, comprised thirteen cases. The typical biochemical findings of obstructive jaundice were constantly present. Very high levels were recorded for serum bilirubin and alkaline phosphatase. The result of the cephalin flocculation test was usually negative. In these cases biopsy examination revealed changes indistinguishable from gall-stone obstruction. Here again mild cholangitis was an early occurrence, though its presence was not always suspected clinically. In some cases it developed into a severe suppurative cholangitis, whilst in others long-standing obstruction failed to produce a severe lesion.

In the latter group there was usually evidence of considerable liver damage. Retention of bile pigment was widespread and the liver cells showed degenerative changes. Cell outlines were ill-defined, staining qualities were poor, and intercellular spaces were widely dilated. That the damage was considerable was supported by biochemical tests, especially impairment of hippuric acid synthesis.

The following three cases are representative of this group.

CASE 47.—E.C., a male, aged forty-nine years, was admitted with a six-months history of dyspepsia. Jaundice had been present for nine days, with clay-coloured stools and dark urine. This had steadily increased. There had been no pain and no recorded fever, but he was reported to have had a rigor on one occasion. He was deeply jaundiced; the liver was just palpable but not tender. Biochemical tests showed that the serum bilirubin level was raised (30 units), bile salts and pigments were present in the urine, hippuric acid excretion was normal (3·1 grammes), the serum alkaline phosphatase level was raised (31 units), the serum proteins were normal and the result of the cephalin flocculation test was positive. An aspiration biopsy specimen taken twenty-seven days after the onset of jaundice was typical of obstructive jaundice with cholangitis and bile pigment retention (see Figure VI). At laparotomy eleven days later the patient was found to have a carcinoma of the gall-bladder obstructing the common hepatic duct.

No calculi were present. A specimen of liver taken from the left lobe revealed aggravation of the features described above. Polymorphonuclear leucocytes were more numerous and in parts were seen as collections within the portal tracts and in the walls of small bile ducts. The patient died four days after operation. Post-mortem section of the liver showed similar changes to those at biopsy described above, but microscopic abscesses were now present.

CASE 51.—H.Z., a female, aged seventy-eight years, suffered from dyspepsia for twelve months and right-sided abdominal pain for six weeks. Jaundice had been present for three weeks, with dark urine and pale stools. The liver was enlarged and the gall-bladder easily palpable. A provisional diagnosis of carcinoma of the pancreas was made. Laparotomy was contraindicated in view of her age and poor physical condition. Biochemical tests showed that the serum bilirubin level was raised (33 units), bile was present in the urine but no urobilin, hippuric acid excretion was impaired (1·0 gramme), the serum alkaline phosphatase level was greatly raised (76 units), and the result of the cephalin flocculation test was negative. Aspiration biopsy forty days after the onset of jaundice showed bile pigment retention, increase in connective tissue and bile duct proliferation in the portal tracts with a small increase in inflammatory cells including a few polymorphonuclear leucocytes. The appearance of the specimen was that of early biliary cirrhosis with a minimum of the cellular infiltration usually present with prolonged biliary obstruction (see Figure VII). The patient died eleven days later. Post-mortem examination confirmed the diagnosis of carcinoma of the pancreas. The liver was enlarged, firm and bile-stained. Microscopic examination showed considerable accumulation of bile pigment in dilated bile ducts and phagocytes, patchy degeneration and atrophy of liver cells and considerable fibrosis, mostly in the portal tracts (see Figure VIII). There was still a minimum of cellular infiltration.

CASE 56.—S.S., a male Arab, aged forty-two years, suffered from abdominal pain, vomiting and jaundice for three months. His urine was dark and his stools clay coloured. When admitted to the Royal Melbourne Hospital on January 29, 1947, he was deeply jaundiced; the liver was enlarged and firm but not tender; the gall-bladder was palpable. A provisional diagnosis of carcinoma of the pancreas was made. Biochemical tests showed that the stools were clay coloured, the urine contained bile pigment and salts but no urobilin, the serum bilirubin level was raised (20 units), the serum alkaline phosphatase level was greatly increased (67 units), there was only slight cephalin flocculation in forty-eight hours, and the total serum protein content and albumin/globulin ratio were normal. Aspiration biopsy (nine weeks after onset of the jaundice) showed that there was considerable cholangitis with accumulation of polymorphonuclear leucocytes in the portal tracts and in the walls of bile ducts. There was slight increase in fibrous tissue.

A laparotomy was performed six days later and the diagnosis confirmed. Cholecystojejunostomy was performed preparatory to a pancreatectomy. An operation biopsy specimen (taken ten weeks after onset of the jaundice) had an appearance similar to that seen in the aspiration biopsy specimen one week previously. There was definite acute cholangitis with polymorphonuclear leucocytes present in the portal connective tissue between the liver cells and in both the lumina and the walls of bile ducts. Pigment accumulation was demonstrable, but fibrous tissue increase was not an outstanding feature (see Figure VIII).

The post-operative course was complicated by mild bronchopneumonia, during which the patient became very debilitated. He then improved in strength and weight and his jaundice diminished. Six weeks after the cholecystojejunostomy a further laparotomy was performed, but the growth was found to be inoperable. A liver biopsy specimen was obtained. In this specimen (taken sixteen weeks after onset of the jaundice) it was not possible to detect any difference from the specimen taken six weeks previously. He died three weeks later, nineteen weeks after the onset of jaundice.

Autopsy.—A limited autopsy was performed and revealed that a contributory cause of death was a subacute intestinal obstruction from pelvic adhesions. The presence of a carcinoma of the pancreas was confirmed; this microscopically was of the columnar-celled type. The liver was of normal size and shape, but tough and deeply bile-pigmented. Its cut surface showed small macroscopic abscesses. On section it was seen that there was an aggravation and extension of the acute cholangitis seen in the biopsy specimen with abscess formation in the portal tracts.

Comment.—This patient was admitted with obstructive jaundice. Cholecystojejunostomy was performed as the first stage of a pancreatectomy. After this the jaundice subsided and six weeks later another laparotomy was performed, when the carcinoma was found to be inoperable. Biopsy specimens were obtained by aspiration preliminary to operation and at both laparotomies. These showed extensive cholangitis with fibrosis which did not show any significant improvement six weeks after relief of the obstruction. This could be attributed to one or more of the following three factors: the infection of the biliary tract may have been irreversible when drainage was instituted, the anastomosis may not have been an efficient means of drainage, or the cholangitis may have been maintained by ascending infection from the bowel especially in the presence of a subacute intestinal obstruction. In spite, however, of the failure in histological improvement, the patient's clinical condition improved. It is interesting to note that post-mortem examination three weeks after the second operation revealed that the cholangitis had progressed and abscess formation was apparent.

Discussion.

From the study of these three groups it seems that in the first group the presence of gall-stones in the gall-bladder without complications was consistent with a liver within normal limits histologically except for a zone in intimate contact with the gall-bladder. The liver was also within normal limits when assessed by available biochemical methods. No great claim is made for this modest correlation of biochemical and histological findings.

In the second group in which a complication had occurred and obstruction of the common bile duct resulted in jaundice, the most common feature was the presence of an inflammatory process in the portal tracts. We have called it cholangitis as bile duct elements are invariably involved. Although characteristic biochemical findings were present, namely, increased alkaline phosphatase, increased bilirubin and bile salts in the urine and impaired hippuric acid synthesis, the only direct correlation of histological and biochemical changes was between serum alkaline phosphatase levels and sections stained for alkaline phosphatase by Gomori's method. Eleven out of twelve patients with elevated serum alkaline phosphatase levels showed histological increase.

It was often possible to anticipate abnormal results of biochemical tests for liver function by examining histological sections, but it was not possible for the prophecy to be quantitative.

It is our opinion that when obstruction occurs the liver damage is sufficient to be detected by biochemical methods and that histological examination goes far to support this observation. The nature of the liver damage is an inflammatory process of the bile ducts and their surrounding connective tissue which is most often characterized by the presence of polymorphonuclear leucocytes. It would be little more than conjecture to say that this inflammatory process was primarily due to bacterial infection or to chemical damage; probably both contribute. The inflammatory process is an incipient suppurative one, but it is often arrested by removal of the obstruction, resolving in a short time to leave little detectable change.

In the group due to obstruction from neoplasm where relief of obstruction is unlikely to occur naturally, liver damage is present and usually progressive. It is important in this group to make use of biochemical tests supported by aspiration biopsy so as to assist the clinician to select those cases which may be amenable to surgery and to indicate cases of infectious hepatitis in which surgical intervention may endanger the life of the patient. Undue delay in cases of jaundice due to continued external obstruction leads to progressive liver damage. In cases of carcinoma of the head of the pancreas, undue delay may militate against the successful removal of the tumour.

Summary.

1. Fifty-nine patients suffering from disease of the biliary tract have been investigated by clinical, biochemical and histological methods.

2. The cases have been divided into three groups—gall-stones without previous history of jaundice, gall-stones

with jaundice or with history of jaundice, and biliary obstruction due to neoplasm.

3. The first group, gall-stones without previous history of jaundice, comprised 23 cases. In four of these there were solitary abnormal biochemical findings, in two positive results of cephalin flocculation tests, in one impaired hippuric acid excretion (1·8 grammes) and in one a raised serum alkaline phosphatase level (35 units). The patients showing these isolated abnormal tests were subjected to cholecystectomy with no untoward results. Histological examination was made of the liver of 15 of the patients. This was within normal limits unless the specimen was obtained from the inferior border of the liver within one inch from the gall-bladder. In this area inflammatory changes were seen commensurate in intensity with those in the gall-bladder and were attributed to the free vascular and lymphatic communication between the gall-bladder and adjacent liver.

4. The second group, gall-stones with jaundice or with history of jaundice, comprised 23 cases; 16 of the patients were admitted to hospital with jaundice and the remaining seven gave a history of jaundice. Of the jaundiced patients 15 out of 16 showed the typical biochemical tests of obstructive jaundice. The serum bilirubin level was raised, bile salts and pigments were present in the urine, there were clay-coloured stools and a raised serum alkaline phosphatase level. Impairment of hippuric acid excretion occurred in eleven out of thirteen cases in which the test was performed. The result of the cephalin flocculation test was usually negative.

In the seven cases of patients with only a history of jaundice the biochemical tests usually found with obstruction were normal, but hippuric acid excretion was moderately impaired. The result of the cephalin flocculation test was negative. Histological examination of the liver of patients who were jaundiced or whose jaundice had subsided in hospital showed cholangitis of moderate to mild severity, even when the specimen was taken from the left lobe.

In the limited number of cases of patients who had not recently been jaundiced there was no evidence of cholangitis in specimens taken from the left lobe.

5. The third group, jaundice due to extrahepatic obstruction by neoplasm, comprised thirteen cases. The typical biochemical findings of obstructive jaundice were constantly present. Biopsy examination also revealed changes indistinguishable from gall-stone obstruction. Mild cholangitis was an early occurrence though its presence was not always suspected clinically. Severe suppurative cholangitis sometimes developed.

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Legends to Illustrations.

FIGURE I.—Case 20. Gall-stones without jaundice. Operation biopsy specimen from right lobe near gall-bladder showing portal fibrosis and round cell infiltration. (See also Figure II.) Hæmatoxylin and eosin × 130.

FIGURE II.—Case 20. Gall-stones without jaundice. Operation biopsy specimen from left lobe. The liver is within normal limits. (See also Figure I.) Hæmatoxylin and eosin × 130.

FIGURE III.—Case 27. Gall-stones with obstructive jaundice. Aspiration biopsy specimen showing cholangitis with openwork appearance and cellular infiltration of portal connective tissue. A few polymorphonuclear leucocytes are present and there is some irregularity of bile duct epithelium. (See also Figure IV.) Hæmatoxylin and eosin × 265.

FIGURE IV.—Case 27. A different area of the same section as Figure III, showing fine connective tissue between liver cells, openwork appearance and cellular infiltration. Hæmatoxylin and eosin × 265.

FIGURE V.—Case 26. Gall-stones with obstructive jaundice. Aspiration biopsy specimen showing black deposits demarcating areas of alkaline phosphatase activity. Serum alkaline phosphatase level raised (30 units). Gomori's stain and methyl green × 300.

FIGURE VI.—Case 47. Carcinoma of pancreas with obstructive jaundice, showing bile pigment deposited in the liver some distance from the portal tracts. Serum bilirubin level raised (30 units). Frozen section, hæmatoxylin and *Scharlach R* × 67.

FIGURE VII.—Case 51. Carcinoma of pancreas with obstructive jaundice. Post-mortem section showing liver cell atrophy and degeneration with considerable amount of portal fibrosis. There is a minimum of cellular infiltration. Hæmatoxylin and Van Gieson × 265.

FIGURE VIII.—Case 56. Carcinoma of pancreas with obstructive jaundice. Operation biopsy specimen showing early suppurative cholangitis. Hæmatoxylin and Best's carmine × 300.

Reports of Cases.

NECROTIZING VASCULAR LESIONS BELIEVED TO BE DUE TO HYPERSENSITIVITY TO SULPHADIAZINE.

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THE introduction of the sulphonamides and their subsequent widespread use led to the discovery that these drugs, beneficial and useful though they were, occasionally produced untoward symptoms. The so-called "toxic" effects of sulphonamide administration include cyanosis, skin eruptions, fever, joint pains and swellings, asthma, granulocytopenia, uræmia, jaundice, hæmolytic anæmia and angina. Of recent years evidence has accumulated to show that some, at least, of these so-called "toxic" effects are manifestations of hypersensitivity. As early as 1937, Hageman and Blake[2] drew attention to the similarity between serum sickness and reactions to sulphanilamide. The fact that in some cases the reaction occurred after the drug had been decreased in dosage, or even discontinued, suggested that sulphanilamide itself, or sulphanilamide in a combined form, was antigenic.

Schönholzer[3] showed that azosulphamide in the blood stream was bound to the serum albumin, and Davis,[4] following the methods of Landsteiner and Lampl, succeeded in conjugating sulphonamide compounds to human blood serum. These results were confirmed by other workers, and Rich[4][5] commented that it was probable that, acting in this manner as haptens, the sulphonamides were able to sensitize the body specifically. Shaffer, Lentz and McGuire[6] reported the production of a positive Prausnitz-Kustner reaction to sulphathiazole with serum from persons who had reacted to the drug a second time. Leftwich,[7] using as test material the serum of patients receiving a sulphonamide drug, elicited cutaneous reactions in 30 persons who had previously shown hypersensitivity to sulphonamide compounds.

Several isolated instances and a few series of deaths due to the effects of sulphonamide drugs have been reported in the literature; according to Black-Shaffer,[11] most of those recorded before 1945 were attributed to uræmia due to accumulations of sulphonamide crystals in the urinary tract, or to the fatal blood dyscrasias, agranulocytosis and hæmolytic anæmia.

Cutts, Burgess and Chafee[8] recorded one death from anuria in a series of patients treated (1940) with sulphathiazole; at autopsy the kidneys showed tubular degeneration with foci of necrosis and interstitial round cell infiltration containing some neutrophilic polymorphonuclear leucocytes. This was one of the earliest cases in which anuria was reported as not being due to mechanical obstruction. Lederer and Rosenblatt[9] (1942) recorded the deaths of four patients during treatment with sulphathiazole. In each instance sulphathiazole was given uninterruptedly. During the therapy a sudden episode of chills and fever occurred, sometimes associated with a rash, conjunctival injection or muscle and joint pains. The symptoms were interpreted as being due to infection and the drug was continued in the original or in increased amounts. The fever persisted, coma developed, and in two cases there was anuria. Histological examination of tissues removed at autopsy showed numerous areas of necrosis scattered throughout most of the viscera with the exception of the central nervous system and the gastro-intestinal tract. In the kidney, in addition to areas of focal necrosis, evidence of severe parenchymal damage was seen. Lederer and Rosenblatt suggested that anaphylaxis might account in part for the non-bacterial foci of necrosis observed.

Merkel and Crawford[10] recorded a similar series of four patients who came to autopsy. The histopathological lesions encountered showed a striking similarity in that they were all areas of focal necrosis, many of which were infiltrated with polymorphonuclear cells. These areas were found in the liver, spleen, bone-marrow, lymph nodes, lungs and kidneys. The clinical histories showed only one common factor, namely that sulphathiazole had been administered. There was a decided variation in the amount of sulphathiazole given and in the duration of sulphathiazole therapy. One patient had apparently acquired a drug sensitivity by taking sulphathiazole in interrupted doses for the treatment of acne.

Rich[4] found recent lesions resembling those of *periarteritis nodosa* in the viscera of five patients who had had serum sickness, following massive serum therapy. He found similar lesions in the tissues of a patient who had received no serum, but had been given repeated doses of sulphathiazole as a prophylactic measure against aspiration pneumonia. Later, Rich[5] described a Negro patient in whom *periarteritis nodosa* developed following a reaction to sulphathiazole. Rich inferred that *periarteritis nodosa* was a manifestation of hypersensitivity and that widely differing antigens might be responsible for its development in different patients. This suggestion had been made by other workers.

Black-Shaffer[11] (1945) reviewed the literature on the pathology of anaphylaxis from sulphonamide drugs, and described five cases of anaphylactic death following the therapeutic use of sulphonamides. Of the five patients two had had sulphathiazole, one had had sulphadiazine and sulphanilamide, one sulphacetamide, sulphadiazine and sulphathiazole, and one sulphanilamide, sulphadiazine and azosulphamide. In general the tissues showed two related lesions: arterial changes and generalized cellular exudate. The arterial changes varied from œdema to necrotizing arteritis, similar to but less intense than the typical lesions of *periarteritis nodosa*. Interstitial myocarditis with an exudate containing large mononuclear cells was found in every instance. Black-Shaffer pointed out that these were among the characteristic lesions of experimental anaphylaxis in animals. In all but one of the patients the underlying disease might have contributed to the picture. He pointed out, however, that many workers had recorded similar lesions in various unrelated disease states in which the only common factor was the administration of sulphonamide compounds.

A. J. French,[12] working at the Army Institute of Pathology at Washington, drew attention to striking histopathological changes seen in the material from 76 autopsies and in two additional specimens of skin taken for biopsy from patients who had apparently been sensitized to sulphonamides. All cases were excluded in which sulphonamide drugs had been given during the treatment of any of the following conditions: septicæmia, rheumatic fever, cardio-vascular disease including coronary occlusion, poliomyelitis, scrub typhus or other proved viral or rickettsial infections, trichinosis, diphtheria, scarlet fever, typhoid fever, or miliary tuberculosis. The changes described included focal and diffuse cellular infiltration of various tissues and vascular lesions characterized by fibrinoid necrosis, endothelial œdema and proliferation. More, McMillan and Duff[14] described the examination of histological preparations from 375 autopsies of patients who had received sulphonamides. In 22 of these they found lesions attributable to sulphonamide medication. As a control series, 400 autopsy cases from the pre-

sulphonamide years, 1930 and 1931, were reviewed. No lesions similar to those described were found in the control series except in association with an ætiological agent known to produce such lesions. They stated that "the lesions encountered in the 22 cases fell into the morphological classification of necrotic, granulomatous, interstitial inflammatory and polyvascular inflammatory groups, and a small miscellaneous group". Polyvascular lesions were found in seven members of the series. Like Rich,[4][6] they laid stress on the great variation in degree of these lesions, and on the fact that they were not specific for sulphonamides but resembled those caused by hypersensitivity to any foreign protein.

Lichtenstein and Fox[12] recorded an instance of death associated with hypersensitivity to sulphathiazole. They found widespread necrotic and vascular lesions, the latter indistinguishable from the classical lesions of *periarteritis nodosa*. It seems probable to us that there was one basic lesion in this case, those described as "necrotic" being "vascular" lesions in which the plane of section had not included the vessel wall. These authors believe that sulphathiazole is the principal offender in respect to hypersensitivity and state that sulphadiazine is preferable for general use. Sulphadiazine, however, was used in the following instance.

Clinical Record.

C.F.C., aged fifty-six years, first consulted his own doctor on or about September 15, 1946, because of fever, malaise and loss of weight. His temperature was found to be 101° F.; the only other abnormal clinical finding recorded was that his urine contained pus cells. There was no history of previous illness. He was given a course of 30 tablets (15 grammes) of sulphadiazine; 2·0 grammes as an initial dose and thereafter 0·5 gramme every four hours for five days. His temperature subsided for a day or so, only to rise again, however, and he continued to have an evening rise to 101° or 102° F. till October 3, 1946, when, as his condition was becoming worse and he was suffering from vomiting attacks, he was admitted to the Royal North Shore Hospital with a diagnosis of pyrexia of unknown origin. There he came under the care of one of us (I.A.B.).

As his mental state was a little confused a full and satisfactory history was not obtained. He appeared to have suffered from loss of weight for one month, epigastric pain and vomiting for one week, and frequency of micturition for two weeks. On examination his temperature was 99° F., his pulse rate 84 and respiration rate 20 per minute. The only abnormality found on examination of the abdomen was epigastric tenderness; the liver and spleen were not palpable. The tongue was slightly furred but moist. The apex beat was in the fifth left intercostal space just outside the mid-clavicular line. The area of cardiac dulness was slightly increased to the left. The heart sounds were regular and of good tone and no murmurs were heard. Blood pressure readings were 140 millimetres of mercury (systolic) and 80 millimetres of mercury (diastolic). There were no abnormal clinical findings in the lungs or central nervous system. There was no record of albuminuria, but microscopic examination showed granular and hyalogranular casts and a few red blood cells and leucocytes. The urine was found to be sterile. The urinary output, with an intake of approximately 60 ounces of fluid, varied from 15 to 30 ounces per day. The blood did not react to the Wassermann and Eagle flocculation tests. The hæmoglobin value was 55% (8·25 grammes per 100 millilitres). The leucocytes numbered 35,400 per cubic millimetre; of these 89·5% were neutrophile cells, 2·5% eosinophile cells, 5% lymphocytes and 3% monocytes.

On the day after admission to hospital (October 4, 1946) the patient complained of some headache and pain in the limbs, mainly the legs. There were no abnormal neurological findings, but as his mental state was somewhat confused and somnolent, lumbar puncture was performed. A cell count of the cerebro-spinal fluid showed 22 leucocytes, mostly lymphocytes, and 22 red blood cells per cubic millimetre. The protein content was 15 milligrammes *per centum*.

On October 9, 1946, five days after admission, an X-ray photograph of the chest suggested a resolving pneumonia of the middle lobe of the right lung. The patient appeared extremely dehydrated, and the blood urea content was found to be 390 milligrammes *per centum*. Intravenous infusion of 5% glucose in normal saline solution was given. The patient's condition deteriorated and he died suddenly on October 12, 1946, at 4.20 a.m., eight days after admission to hospital. During the time that he was in hospital his temperature did not rise above 100·6° F., being mainly around 99° F., while his pulse rate averaged 90 per minute, increasing to 110 per minute just before death. Sulphonamides were not administered during his stay in hospital.

Autopsy Report.

The body was that of a thin, elderly man. All the tissues of the body were anæmic. The brain weighed 1350 grammes and was œdematous. The lungs showed some œdema, and patchy congestion, most marked at their bases. The left lung weighed 548 grammes, the right lung 590 grammes. The heart was enlarged, weighing 420 grammes; the enlargement was due to dilatation and to œdema of the heart wall. The aorta was slightly dilated and the intima showed areas of yellowish thickening. No ulceration or calcification was found. The coronary arteries appeared normal macroscopically. The peritoneal cavity contained about 400 millilitres of clear fluid and the retroperitoneal tissues were œdematous. The liver showed no gross abnormality. The gall-bladder was thin-walled and contained bile; the bile passages were normal. The spleen was enlarged, weighing 14·5 ounces (408 grammes); it was moderately firm and the surface was mottled in red and white, apparently by patchy thickening of the capsule. The cut surface showed an increased amount of fibrous tissue. The mucous membrane of the stomach and duodenum showed enlarged veins and petechial hæmorrhages. No ulcer was present. The kidneys were much enlarged; the left weighed 10 ounces (280 grammes); the right 14·5 ounces (408 grammes). They were essentially similar. The capsules were thickened, the surfaces pale, with petechial hæmorrhages. The cut surface showed swollen, cream-coloured cortex contrasting with reddish-purple, congested pyramids. The prostate was small and showed no macroscopic abnormality.

The great enlargement of the kidney at autopsy was partly due to œdema; there was considerable shrinkage during fixation, though the preserved specimen was still much increased in size.

Histopathology.

Histological examination of the kidney showed a most unusual picture. The cortex was increased in extent and was almost completely occupied by closely packed or confluent foci of inflammatory cells having a central area of necrosis or surrounding a necrotic vessel. The essential lesion was a subacute necrotizing arteritis; we consider that the necrotic lesions were vascular lesions in which the plane of section had not included the vessel wall. Frequently there was almost complete necrosis of the wall of a small or moderate-sized artery; surrounding the necrotic vessel were large numbers of polymorphonuclear leucocytes including some eosinophile cells and also plasma cells, lymphocytes, mononuclear and spindle-shaped cells. The destruction of the cortex was so complete that there was hardly a normal glomerulus left and only a few distorted tubules. Many similar lesions were found in sections of the spleen, which no doubt contributed to its enlargement, and an occasional lesion of somewhat similar type was seen in tissue taken from the lower lobe of the left lung, which showed also cellular infiltration and thickening of the interstitial tissue. The heart showed interstitial myocarditis, with œdema and cellular infiltration of the perivascular tissue; the muscle fibres were separated and fragmented in places and a sparse interstitial monocytic infiltration was present. No necrotizing vascular changes were found in the liver; there was, however, diffuse cellular infiltration of the parenchyma and of the portal tracts. Sections of the sternal bone-marrow showed a hypercellular, hyperplastic marrow, with

occasional large collections of lymphocytes. In some areas eosinophile cells were very numerous. No organisms were found in sections of liver, spleen and kidney stained by the eosin-Gram-Weigert and Ziehl-Neelsen methods.

Discussion.

The diagnosis in this case was not at first apparent. Histological preparations were sent to the Department of Pathology of the University of Sydney and Professor Keith Inglis suggested that the necrotizing arteritis might be due to hypersensitivity to sulphadiazine and referred us to the work of French,[12] Lichtenstein and Fox,[12] and More, McMillan and Duff.[14] Later, preparations of kidney and spleen were sent to the last-mentioned authors in Toronto, Canada, and a letter from Professor G. Lyman Duff was received stating that he and Dr. McMillan were convinced that the lesions found were attributable to sulphonamide sensitivity; that they were exactly the same in kind as in the cases that he and his colleagues had studied, but were more intense and widespread. As far as one can gather from the available literature, the changes in the kidney in this patient were more acute and widespread than in most other recorded instances. Practically the whole of the cortex of both kidneys was destroyed. The possibility that the lesions existed before treatment with sulphonamide cannot be entirely ruled out, but seems very unlikely. Interstitial myocarditis of a type similar to that attributed to sulphonamides by other workers[11][15] was present. The patient's history does not suggest preexistent *periarteritis nodosa*. The lesions do not resemble those due to any known infective agent and no organisms were found in specially stained sections.

Untoward symptoms have followed the administration of sulphonamide in amounts ranging from eight to 340 grammes, and multiple courses of therapy separated by intervals varying from hours to weeks have appeared to result in acquired sensitivity. However, no one could have foreseen the tragic outcome of treatment in the case history reported here; the patient had had no previous illnesses and there was no contraindication to the giving of sulphadiazine. Instances of fatal sulphonamide allergy are, of course, extremely rare, and in serious illness the benefits of sulphonamide treatment may far outweigh the risk of sulphonamide allergy. As to the lessons to be learnt, French[12] states that increased caution should be observed in the prophylactic and therapeutic use of the sulphonamide drugs for minor infections. Patients to whom these drugs are being given should be observed carefully so that any sign of hypersensitivity may be detected as early as possible. Every advance in knowledge seems to bring difficulties and dangers in its train, but these may point the way to fresh discoveries, and the study of hypersensitivity to sulphonamides may be of great importance in increasing our knowledge of the pathology of allergy in man.

Summary.

1. Some of the literature relating to hypersensitivity to sulphonamides is briefly reviewed.

2. The case-history of a patient with uræmia and necrotizing arteritis possibly due to hypersensitivity to sulphadiazine is presented.

Acknowledgement.

We wish to record our thanks to Professor Inglis for help and advice in reporting this case and also to the Department of Pathology of the University of Sydney for preparing the photomicrographs which accompany it.

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Legends to Illustrations.

FIGURE I.—Longitudinal section of kidney, showing swollen, cream-coloured cortex, contrasting with dark, congested pyramids.

FIGURE II.—Photomicrograph of kidney. Portion of a large artery is included; the upper third does not show necrosis of the wall, and this part was continuous (in the section) with a considerable length of artery free from necrosis. The lower two-thirds show necrosis of the wall with some bulging in the middle third. × 50.

FIGURE III.—Photomicrograph of kidney, showing a medium-sized vessel with much necrosis in the wall; polymorphonuclear leucocytes are abundant in the surrounding inflammatory zone. × 100.

FIGURE IV.—Photomicrograph of kidney showing another vessel (possibly a continuation of that represented in Figure III); polymorphonuclear leucocytes are conspicuous in the surrounding inflammatory zone. × 200.

Reviews.

OPHTHALMOLOGY.

THE fourth edition of the late Sanford Gifford's well-known textbook of ophthalmology has been revised recently by Francis H. Adler, Professor of Ophthalmology in the University of Pennsylvania.[1] It is intended for the practitioner not specializing in ophthalmology, as a "working basis" for the medical student and as a "reference book for the later years of practice".

In the opening chapters on the examination of the eye the ophthalmologist will find as much to interest him as the medical student, and nothing that is not sound. A chapter of fifty pages deals in masterly fashion with the disturbances of ocular motility, and the physician and neurologist will find it a valuable source of reference. Adler has little use for orthoptics in the treatment of heterophoria and squint.

The "bread and butter" of the ophthalmologist, the prescribing of glasses, is presented with rare common sense. It is unfortunate that the writer clings to the use of the word "eye-strain". Were the term abolished, it is not improbable that most opticians would be forced to close their shops, and the ophthalmologists to revert to general practice. He advocates a policy of common sense in the treatment of myopia and in the prescription of glasses. As there is no evidence that the use of the eyes leads to an increase of myopia, he points out the futility of restricting

[1] "Gifford's Textbook of Ophthalmology", by Francis H. Adler, M.D.; Fourth Edition; 1947. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9½" × 6", pp. 526, with many illustrations, some of them coloured. Price: 42s.

the visual activities of the young myope. In spite of his warning, ophthalmologists will continue to strike terror into the hearts of their young patients with "weak eyes" and government departments will refuse to accept myopes as candidates for superannuation.

After digesting a short chapter on exophthalmos, the physician will be tempted to peruse the remainder of the book describing those diseases which are in the private domain of the eye specialist—iritis, glaucoma and their allies. Alluding to the impossibility of defining the exact cause of so many types of inflammation of the uveal tract, the author gives a warning against the wholesale eradication of "septic foci" on mere suspicion. Australian ophthalmology will be particularly gratified at his recognition of the brilliant work of Gregg, of Sydney, in demonstrating the link between maternal rubella and congenital cataract.

It is difficult to find fault with a work in which the author gives a précis of a comprehensive subject in such a masterly fashion. The book can be well recommended to the general practitioner as a concise, sound and up-to-date source of reference for diseases of the eye.

A YEAR BOOK OF UROLOGY.

IT is pleasing to see "The Practical Medicine Year Books" regaining their object of providing a comprehensive summary of significant contributions to the year's medical literature, and "The 1947 Year Book of Urology" has quite a notable proportion of material taken from British and Continental journals.[1] Edited as in the past by Oswald S. Lowsley, this book maintains its high standard of subject matter and production. The general arrangement has not been altered; a section on general considerations opens the volume, followed by sections concerned with the main anatomical subdivisions of the uro-genital tract and separate sections on transurethral operations and gonorrhœa. The literature dealt with is succinctly presented with only occasional brief but relevant editorial comment and seems to refer to practically every aspect of the general subject. Individual subjects are not easily picked out, but appearing fairly prominently are several papers on the treatment of anuria by peritoneal irrigation, a procedure still to be approached with a good deal of caution; further reports on streptomycin indicate its limitations and its value, if rightly used, in genito-urinary infections; much ingenuity is displayed in the surgery of the ureter, including the use of tantalum tubes; a good deal of space is devoted to bladder tumours and to transurethral resection of the prostate with special reference to the occurrence, as a complication, of hæmolytic reactions; and the place of endocrine therapy in carcinoma and other disease of the prostate is discussed. There is a great deal else and some of it will be already known to those who read their journals. However, it is safe to say that anyone who is interested in urological problems will find at least something to help him in this useful publication.

FUNDAMENTALS OF IMMUNOLOGY.

THE second edition of W. C. Boyd's "*Fundamentals of* Immunology" follows closely after a reprinting of the first edition, thus bearing testimony to the usefulness which it serves.[2] The new volume has several improvements in the arrangement of the text. The type is uniform in size, the "small print for advanced students" has been abandoned, and excellent summaries are appended to each chapter, the ease with which particular points may be located, in the text being thus materially increased. A large proportion of the added 57 pages is absorbed in the expansion of the lists of references at the end of each chapter.

The earlier chapters of the book have been extensively rewritten, and it is pleasant for Australian eyes to see an appreciation of Professor Burnet's views and of his book "Biological Aspects of Infectious Disease". The present-day knowledge of antibodies and their physico-chemical behaviour is responsible for the introduction of new discussions of molecular size and shape of the serum globulins, and the increasing importance of the information to be gained from studies of electrophoretic mobility by the method of Tiselius. This influences the chapter on antigens, where the consideration of physical factors replaces part of a large section on conjugated antigens, and leads to a consideration of the relation between the number of reactive groups in the antigen molecule and the number of antibody molecules with which it can combine—its valence.

The succinct definition of a toxin as an "antigenic poison" is a valuable one, and should be emphasized to clinicians in their unthinking use of this much abused word.

The chapter on blood groups contains one error which cannot be allowed to go unnoticed—the scant mention of "data published in the Australian Journal of Medicine" refers, we presume, to the excellent work of Simmons *et alii* and R. J. Walsh and his co-workers (which deserves more recognition) and the "Journal" is THE MEDICAL JOURNAL OF AUSTRALIA and *The Australian Journal of Experimental Biology and Medical Science*.

The chapter on complement fixation has been brought up to date, and contains a discussion of the fractionation of complement and the activities of the various portions. Careful reading reveals on almost every page some small addition to the text, and shows with what care the author has prepared the new edition. Workers in the field of immunology cannot afford to be without it.

HISTOLOGY.

"A TEXTBOOK OF HISTOLOGY FOR MEDICAL STUDENTS", by Evelyn Hewer, has now reached the fourth edition in a period of ten years since it was first published.[1]

While the book serves as an introduction to histology, it provides an adequate account of the essential details of histological structure. The photography, generally, is excellent and this edition contains many new photomicrographs of specimens obtained from human material. A short new chapter on protective mechanisms in the body has been added; it is doubtful if in a book of this type such a chapter is of any value. Since the matter in this chapter is only "suggestive rather than exhaustive", it would have been better to present the suggestions as the histology of the various systems is described. There is a classification of the various usual sources of entry of injurious substances into the body; it is doubtful if one should look upon a damaged gut wall as a usual source of entry. Certainly it should not be regarded in the same way as one regards the entry of dust particles into the respiratory tract.

Some of the diagrams and drawings are difficult to follow, but generally they are useful. They are especially valuable in the chapter devoted to the central nervous system; here they are used to simplify the fibre tracts and nuclei seen in the photographs of cross sections of the brain stem at different levels. These diagrams and photographs alone would render the book valuable to most medical students.

The book adheres to Dr. Hewer's original intention—to serve as an introduction to histology—but the keen medical student will then have to go further afield to appease his appetite.

A TEXTBOOK OF MEDICINE.

WHEN it is considered that the first edition of G. E. Beaumont's "*Medicine: Essentials for Practitioners and* Students" was published only six years ago, the recent arrival of the fifth edition is proof of its popularity.[2]

Dr. Beaumont is a clinical teacher, and his main objects were to produce a textbook of medicine which was not too long for the final year student, yet would be useful also to the general practitioner. The latest edition has been successfully brought up to date almost solely by the efforts of the author himself—a Herculean task.

The book remains at much the same size as its predecessors (786 pages). This has been accomplished by the deletion of obsolete sections. Among the new articles reference may be made to descriptions of the following: fibrocytic disease

[1] "The 1947 Year Book of Urology", by Oswald S. Lowsley, M.D., F.A.C.S.; 1948. Chicago: The Year Book Publishers Incorporated. 7" x 4½", pp. 414, with illustrations. Price: $3.75.

[2] "Fundamentals of Immunology", by William C. Boyd, Ph.D.; Second Edition; 1947. New York: Interscience Publishers Incorporated. London: Interscience Publishers, Limited. 9" x 6", pp. 518, with illustrations. Price: $6.00.

[1] "Textbook of Histology for Medical Students", by Evelyn E. Hewer, D.Sc. (London); Fourth Edition; 1947. London: William Heinemann (Medical Books), Limited. 9¼" x 6¼", pp. 516, with many illustrations. Price: 21s.

[2] "*Medicine: Essentials for Practitioners and Students*", by G. E. Beaumont, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (London); Fifth Edition; 1948. London: J. and A. Churchill, Limited. 9" x 6", pp. 848, with many illustrations, some of them coloured. Price: 30s.

of the pancreas, erythroblastosis, infective hepatitis, homologous serum jaundice, primary atypical pneumonia, carcinoma of the prostate treated by œstrogens, scrub typhus, and the treatment of thyreotoxicosis by thiouracil. Many sections have been rewritten and contain the essentials of recent work. The newer drugs, including penicillin, "Benadryl", DDT, folic acid, the radio-active isotopes and streptomycin are briefly reviewed. No references are given, as these would necessarily increase the size of the book; but there is a good index, the print is clear, and the book is well produced. The description of each disease includes the clinical findings, and although these are brief, they are clear, and give a mental picture more easily retained by the student than long rambling dissertations. Perhaps brevity is taken to the extreme in some instances; yet it cannot be denied that the essentials are here. It is difficult to think of any important new work that does not at least receive mention.

The book follows the standard practice of describing diseases as they affect the various systems of the body. Dermatology and psychiatry are not included. Descriptions of the diseases which affect the nervous system occupy 163 pages, those of the cardio-vascular system 76, of the respiratory system 92 and of the alimentary system 118. Tropical diseases are also included.

This book succeeds in what its author intended—namely, in describing the essentials of medicine. It will retain its useful place in the libraries of students and practitioners.

VENEREAL DISEASE.

"VENEREAL DISEASE: ITS PREVENTION AND CONQUEST" is a small book of eighteen brief chapters by George Ryley Scott.[1] It has been written for men and women in general from the period of adolescence onward.

The effect of venereal disease upon a civil population, as well as its possible crippling effect on an army in time of war, is mentioned, and included in the first chapter is a statement suggesting that roughly one in every ten persons in the United States of America suffers from syphilis. This statement is open to challenge, in view of the selectee syphilis rates in the United States during the last war which gave an indication that about 2·4% of the general population might be regarded as the closest estimate of the true prevalence of syphilis so far made.

Venereal disease is claimed to be "public health and efficiency enemy No. 1" and hope for its control to be warranted only if the problem is approached as one of disease and not as one of morals or ethics.

A brief and undetailed description is given of syphilis and gonorrhœa, and mention is made of some methods of treatment: "Neosalvarsan" is misnamed "909" when it should be "914". The methods are not completely up to date, but this is of minor importance as they are only alluded to and not detailed. Mention is made of the problem of prostitution. Promiscuity rather than prostitution is regarded as the major factor in the spread of venereal disease, and those responsible are not considered prostitutes according to law, but females who engage in promiscuity not necessarily for money or presents, but often merely for pleasure.

It is stated that it is impossible to regulate prostitution in any complete sense or to abolish it, and it is claimed that "the first evil which increases as professional prostitution diminishes is the promiscuity of so-called respectable girls; the second is the increase in cases of rape and assaults on children; the third is the extension of homosexual vice and other perverse practices".

In regard to compulsory notification the author sums up against it as "any system of compulsory notification and treatment of venereal disease is bound to defeat its own ends" and it would be a serious interference with personal liberty. He quotes in support of his contention that in Australia in 1922 at a medical conference of the Commonwealth and States called to consider the question of compulsory treatment of venereal diseases, "it was admitted that there was no evidence to show that such compulsion had resulted in any reduction of the prevalence of congenital venereal infections". Much has happened in Australia since that opinion of a quarter of a century ago, and congenital venereal infections are uncommon today. While it is true that notification in respect of private and hospital patients is not equally successful, yet, as the vast majority of those infected seek treatment at public centres, the notifications received from such centres give a fairly accurate idea of the rise and fall of infection in the community.

Looking back over many years one might truly claim that notification has served a useful purpose, for not only has it enabled one to estimate conditions, but it has also helped to keep more patients under treatment until non-infective than would have been the case without legislation.

The author also objects to Regulation 33B which was a British defence regulation during wartime which enabled alleged sources of infection to be followed up under certain conditions. In Australia the National Security (Venereal Diseases and Contraceptives) Regulations had a similar function, but gave wider powers. They were useful and helped to bring many infecting sources under control. If a person is found with a venereal disease it appears only reasonable to seek the source of infection and bring it under control. Legislation is necessary for this action.

Ryley Scott appears to object to any legislation aimed at the control of venereal disease as "there would appear to be insufficient evidence of its reported beneficial effects to justify so serious an interference with personal liberty". Our experience does not agree with this opinion. He depends on uncontrolled individual action for the prevention of infection. Abstention from promiscuous intercourse is regarded as the only certain method by which infection may be avoided. Next comes the avoidance of accidental infection and the destruction of microorganisms responsible for infection when a risk has been taken.

Methods of chemical and mechanical prophylaxis, for men and women, are discussed in some detail, and potassium permanganate solution and calomel ointment are advocated as prophylactics. If a condom is used it is recommended that the protection it may afford should be supplemented with chemical prophylaxis. No mention is made of serological tests for syphilis prior to marriage, or at pregnancy, though such procedure helps to arrest the spread of disease. Nor is mention made of the need for sex education of the young so that they may come to adult years with protective knowledge and disciplined in self-control.

The book is of value in its particular field and may be recommended as one containing much useful information.

[1] "Venereal Disease: Its Prevention and Conquest", by George Ryley Scott, F.Ph.S. (England), F.Z.S.; Second Edition; 1947. London: Torchstream Books. 7" × 4½", pp. 80. Price: 3s. 6d.

PARANASAL SINUSITIS AND CHRONIC ILL-HEALTH.

"CHRONIC ILL-HEALTH RELIEVED BY DRAINAGE OF THE PARA-NASAL SINUSES" is a little book by Rosa Ford.[1] It is dedicated to the general practitioner as well as to the ophthalmic and rhinological colleagues of the author who held the position of ophthalmic surgeon to the South London Hospital for Women. The book contains many case histories to illustrate the author's contention that much ill health is due to unrecognized inflammation of the nasal sinuses. She is certainly on sound ground in her assertion of the six fallacious theories which lead to neglect of treatment of the sinuses in many pathological conditions. These fallacies are: that a nose clinically normal is proof of the absence of sinusitis; that unless pus can be demonstrated there is no sinusitis; that a "negative" radiological report excludes sinusitis; that if irrigation of a sinus returns no pus there is no sinusitis; that thickened mucous membrane does not necessarily indicate active infection; that persistent nasal or post-nasal catarrh, even if purulent, may be due merely to naso-pharyngeal inflammation. Further, the author deprecates the tendency to limit workers in diagnosis to water-tight compartments instead of active teamwork. The human body is indivisible. Success is claimed for treatment based on paranasal sinusitis as the predisposing cause of such illnesses as rheumatoid arthritis, disseminated sclerosis, duodenal ulcer, coronary thrombosis, *tic douloureux*, and a great many eye conditions. Special emphasis is laid on the necessity for determining the fields of vision in every case, as a contracted field of vision is, in the author's opinion, a most important indication of sinusitis. She goes so far as to remark that in her series of cases contraction of the fields of vision was the only indication upon which successful treatment of the main condition was based. The treatment used by the author varies from the simplest inhalations to radical antrostomy, and other surgical drainage. This book is certainly well worth perusal in order to reorientate our views of cause and effect in a large number of distressing ills which are far too frequently dismissed by the practitioner as in the category for which "nothing can be done".

[1] "Chronic Ill-Health Relieved by Drainage of the Para-Nasal Sinuses", by Rosa Ford, M.B. (London), D.O. (Oxon.); 1948. London: Henry Kimpton. 7¼" × 4½", pp. 116. Price: 6s.

The Medical Journal of Australia

SATURDAY, JUNE 5, 1948.

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THE MENTAL HOSPITALS OF NEW SOUTH WALES.

PERUSAL of the annual report of a mental hospitals department is always certain to arouse interest, but that interest is almost invariably accompanied by a feeling of hopelessness and futility. In March last year in an article in these columns entitled "The Tragedy of the Mental Hospitals" special attention was directed to the report of Dr. J. Catarinich, Director of Mental Hygiene of the State of Victoria, and to the heart-breaking conditions reported by him. Reference was also made to some of the conditions prevailing in New South Wales mental hospitals as well as to certain statements in the report of the Board of Control in Great Britain. It may be asked what good is done by repeated annual reference to the shocking state of these institutions. There is admittedly a temptation to desist, to accept futility, or to assume a cheerful belief in recurring promises of better conditions that are always waiting just round the corner. But this would be useless. The insane cannot raise their own voices in protest, they cannot make demands on the "sitting member" who is supposed to represent them in "the House". Until the plea for proper accommodation and nursing treatment of the insane is taken up by the Press with ceaseless demand, by public bodies of intelligence and by individual citizens and improvement is effected, this journal must continue its unpleasant duty of dissecting reports and of proclaiming the rights of the mental patient.

The report of the Inspector-General of Mental Hospitals of New South Wales for the year ended June 30, 1946, was ordered to be printed on October 23, 1947, and was received by us in March, 1948. The date on which the report was submitted to the Minister was March 21, 1947—nearly nine months after the period with which it deals had elapsed. Seven months then passed before the order for printing was given. They do things a little more quickly than this in England. The Report of the Board of Control, Part I, which deals with the year 1946, was presented in June, 1947, and was ordered to be printed on July 4, 1947; a copy was received early in February, 1948. The New South Wales report is short, but as sad as it is short. It is sad in what it tells us and sad in what it leaves untold. The total number of patients in residence, including voluntary patients and inebriates, was 11,054. The number of new admissions of certified patients from July 1, 1945, to June 30, 1946, was 1437—this was an increase of 113 on the figures for 1944-1945. Readmissions totalled 256. Of the 1437 patients who were admitted to the department's institutions, no less than 1318 came as voluntary admissions. Excess accommodation exists at three institutions—Broughton Hall, Gladesville and Kenmore—for 110 patients; in the other institutions there is overcrowding of 1667 patients. This number is enormous, and it does not require a great deal of imagination to visualize conditions which must exist in such an institution as that at Orange where there is accommodation for 1166 patients, but 1597 are in residence—431 have to put up with some kind of make-shift. In the face of this we are asked to swallow the cheerful statement that: "It is anticipated that the overcrowding in Mental Hospitals will be eliminated in the very near future, when various schemes which have already received approval are implemented." One may be forgiven for asking: "How near is 'very near'?" The paragraph following the words just quoted is revealing: "Finality has not yet been reached in regard to a new metropolitan hospital, or for the provision of a hospital of the Farm Colony type. Plans for a Convalescent Hospital in the Port Stephens District are proceeding, however, and it is confidently anticipated that such a hospital will soon be provided." This statement is followed by a list of remodellings, additions and alterations at seven institutions which have been submitted to the Public Works Department for execution. This is splendid; however, "shortage of materials and labour is retarding the commencement of the majority of these works, but every endeavour is being made to overcome these difficulties".

Turning to the general care of patients, we find that owing to the "great shortage in female nursing staff" and "the serious overcrowding in the mental hospitals generally" (this admission is frank enough to arrest the attention of any Minister of the Crown) "it has not been possible to give the patients the efficient care and supervision which has been the standard in previous years". It is useless to follow that statement by another which is obviously true: "However, it is expected this difficulty will be overcome when the staff conditions return to normal and the works referred to previously in this report can be carried out." Shortage of female staff is not new in this department, any more than it is new in any other mental hospital department. One would expect to find some information about numbers of female mental nurses and also some details about what efforts are being made to obtain additional nurses. It would be interesting to know whether the shortage has anything to do with remuneration, and if so, whether any allowance is made for the performance of unpleasant duties in the nursing of certain types of patient. We read that most of the mental hospitals are equipped with electro-shock apparatus for the treatment of patients. Apparently some of this work is done in spite of the shortage of nurses. The results are set out in four tables covering four pages. The numbers are interesting. In only four of all the groups in the different hospitals are the totals over 100. The actual numbers of patients "recovered", "relieved", "not improved" and "died" are given; but the mistake is

made of expressing the figures for these first three categories in percentages. For most of these groups the percentages are worthless, but beyond this it looks a little odd to see a single patient in one group who manifested no improvement branded as 100% not improved. We also read that occupational therapy has had to be curtailed for lack of material, but "it is anticipated" that shortly an increased supply of materials will allow many of the occupations to be resumed.

Some of the main features of this report have been mentioned. The financial side has not been referred to. It must suffice to state that the average cost per patient *per annum* is £89 8s. 11d., having risen to this level in ten years from £63 7s. 1d. A certain amount is collected each year for maintenance by the Master in Lunacy and money is obtained by the sale of meats, fat, old stores, farm produce and so on; the total cost of the maintenance of patients is, however, over £1,000,000 a year. It is clear from the items selected from the report that the whole staff of the Mental Hospitals Department labour under great difficulties. We have no doubt they do their best; and this is also true of the Inspector-General, who cannot be held responsible for the Cinderella-like treatment meted out to his department. We think that his report is too mild and far too hopeful of the fulfilment of government promises for building.

Current Comment.

HOT DRINKS.

THOUGH there are vague ideas about the optimal temperature for hot drinks there does not seem to have been much if any effort made to find out what temperature is preferred by most men and women. J. N. Hunt, apparently inspired by a suggestion in a standard textbook on surgery that women are more prone to post-cricoid carcinoma than men because they drink their hot fluids at a higher temperature than men, has carried out an experiment on healthy students.[1] The subjects were students attending sessions of practical work in physiology during the autumn and spring terms. The method followed was simply to give each man or woman an earthenware cup containing beef extract to which boiling water had been added. The student sipped the drink from time to time, and when it had reached a temperature at which he usually took hot drinks, it was taken back to a supervisor who took the temperature, always using the same thermometer. Repeated observations were made at intervals of a week. In this way the thermal preferences for drinks of 149 women and 87 men were determined. Considerable divergences of taste were found, the range being from 54° to 76° C., but two-thirds of the readings fell between 54° and 66°. Statistical analysis showed that the means were 60° for men and 61° for women, the standard error being less than 0·3 in each instance. There appears to be no probability that the means show any significant difference. Hunt remarks that it is surprising to find that a figure so high as 60° C. was chosen by these people, seeing that the highest tolerable temperature for a hot bath is 43° C. The mean difference between the highest and the lowest readings for each subject was less than 5°, which indicates that individual preference in this matter is confined within very narrow limits. The classic instance of malignant change induced by heat is given in textbooks as the skin cancer of the natives of Kashmir, thought to be caused by the prolonged application of a pot of hot charcoal. This was discussed in this journal on June 14, 1941. The other instance of the effect of contact of a hot clay pipe would be difficult to check now, though there seems little doubt that repeated trauma of some kind or another is a determining factor in the local incidence of some types of malignant disease. Surely in the instance quoted of the pharyngeal cancer an unwarranted statement has been made, even if only as a suggestion. The sex incidence of disease is a mysterious thing in medicine, for sometimes it seems inexplicable. However, the experiment is of some interest, though whether the subjects represent a true sample of the community or not is another matter. It might perhaps tend to produce a slightly higher temperature in the tests if the subjects are waiting for the liquid to cool. But these speculations start so many notions, social and domestic, especially in the world of today when men have more to do with culinary details than of yore, that it is better to desist, and leave the experiment at its cool or warm scientific level.

[1] *Guy's Hospital Reports*, Volume LXII, 1947.

CAPILLARY FRAGILITY AND THE USE OF RUTIN.

RUTIN is one of the recent introductions into therapeutics. Derived from the buckwheat plant in 1860, and since found in other plants, it has been shown to have value in the treatment of hæmorrhagic states due to capillary fragility. Clinical reports have been favourable in hæmorrhagic episodes in several different types of vascular disease, though the optimism of these observers has not been shared by all. Leon M. Levitt, M. R. Cholst, R. S. King and M. B. Handelsman have recently published a study of twelve diabetic patients with increased capillary fragility in whom the existence of retinal hæmorrhages gave the inquiry special point.[1] As a preface to their account they give a summary of the conditions in which capillary fragility occurs. Infections, states associated with thrombocytopenia, scurvy, skin diseases, tuberculosis in children, hypertension and a variety of toxic states are among the varied collection of conditions in which this vascular anomaly may be found. The pathological mechanism is not always the same, as a blood vessel may rupture owing to a number of different causes, and blood may penetrate the wall of a vessel by diapedesis due to changes in the endothelium, or in the elastic tissue, or in other pericapillary supporting tissue. It is therefore evident that a treatment successful in one case may be quite ineffective in another. Levitt and his co-workers mention six different tests which have been used to establish the existence of pathological fragility of the capillary vessels. It is not surprising that the evidence gained from these is often conflicting. The method adopted in their own work was that of positive pressure, applied by a sphygmomanometer armlet, the appearance of petechiæ being watched for below the band. As the subjects of this study were diabetics, and the particular interest in their vascular state depended on the occurrence of retinopathies, the authors summarize the evidence for the existence of increased fragility in diabetics, and the connexion between this and retinal accidents. There seems no doubt from the literature that decreased capillary resistance is common among diabetics, though the percentage (41) reported by a famous authority like Joslin is not so high as that found by some other workers. Diabetics who have hypertension are very frequently found also to have an increase of capillary fragility, and naturally this is more frequent in the fifth and sixth decades. Patients with retinal lesions appear to be frequently the subjects of capillary fragility as evidenced by tests.

In the present series twelve diabetics were studied who had retinal hæmorrhages and who also showed a well-marked increase in the fragility of their capillary vessels. They all received routine treatment to control their diabetes, all but one being given insulin. For one month before the special treatment began they were saturated

[1] *The American Journal of the Medical Sciences*, February, 1948.

with ascorbic acid, a dose of 100 milligrammes three times a day being given. Then 20 milligrammes of rutin were given three times a day for two months, and double this dose for another month. Five patients took ascorbic acid throughout the whole period. The results were not very striking. Capillary fragility decreased in only three out of the twelve to any substantial degree. Improvement was noted in the fundal condition of only five eyes out of the twenty-four examined, and two of the patients who showed such improvement had no change in their general capillary state. In one patient diabetic retinitis regressed while under observation. The authors do not think that clearing up of the retinal damage, which occurred in two eyes, can be attributed to the use of rutin. As they rightly remark the ætiological agents in diabetic retinitis are not simple or single. Perhaps it is too much to expect the administration of a glucoside like rutin to work miracles. All that has been established about it is that it may have the effect of reversing certain tendencies towards functional inefficiency of the capillary walls, but where irreversible changes have taken place too much cannot be expected. The thieving pathological processes which steal our health do not always need an unlocked door to the stable; they seem to be able to pick the lock under our eyes.

METAMORPHOSIS OF AMPHIBIA AND THE RETICULO-ENDOTHELIAL SYSTEM.

FIFTY years ago the English physiologist Swale Vincent removed the spleen from a number of puppies, both male and female, and kept the animals for their full term of years. The dogs led a perfectly normal life and produced healthy offspring, and Vincent suggested that whatever functions the spleen performed, it was not the only organ capable of carrying these out. Since that time the importance of the reticulo-endothelial system has come into increasing prominence, but though much has been learned this story has by no means had its last chapter written. The participation of the reticulo-endothelial system in the formation of antibodies has recently been stressed by A. Fagraeus[1] and an explanation has been sought in this same complex for the fact which has long puzzled pharmacologists, namely, that certain drugs act vigorously on invading organisms *in vivo* in concentrations far below those which show appreciable inhibiting power *in vitro*; it is assumed, for example, that antisyphilitic agents owe most of their efficiency to stimulation of the reticulo-endothelial system. Apart from obviously pathological states the reticulo-endothelial system is continuously active in healthy life, and indeed it has been said that probably there can be no process in the organism without some reaction in this structure.

A recent contribution to the study of this scattered tissue deals with what may be regarded as a very minor aspect of the general problem, and that is the induction of metamorphosis in amphibians. Zbigniew Stuchly, a Polish investigator, experimented with axolotls which do not normally change over from water-breathing to air-breathing unless some special conditions arise.[2] As is well known, the reticulo-endothelial system can take up foreign and indifferent dispersed matter, mostly electronegative, such as India ink, carmine, pyrrhol blue and the like; the amount of the colloid introduced into the circulation can be sufficient to put the system out of action—it is then said to be "blocked". If the blocking factor ceases to be introduced, then, after a certain time, the organism starts to free itself of the intruder. Colloids or finely dispersed matter act as a stimulus, however chemically inert they may be. Now metamorphosis in the amphibian involves both destruction of old organs and the formation of new of a totally different type. Stuchly discovered that partial blocking of the reticulo-endothelial system with quite indifferent colloids, such as India ink, precipitated the axolotl into metamorphosis. He postulates a stimulation of the system by the partial block and has come to the conclusion that the reticulo-endothelial system is the immediate performer of the process, though admitting that this is not the whole story, for the autonomic system and the endocrine glands, especially the thyreoid, have some say. Though the research is incomplete, a sufficiently large number of experiments has been conducted to prove his contention that axolotl metamorphosis can be induced at will by the partial blocking of the reticulo-endothelial system through any colloidal agent not in itself directly stimulating to any part of the nervous system or to any recognized endocrine gland. Such a research may not at first sight appear to impinge on human physiology, pathology or therapeutics; but who dare prophesy that this may not be the case?

[1] *Journal of Immunology*, Volume LVIII, 1948, page 1.
[2] *Annales Universitatis Mariae Curie-Sklodowska*, Volume II, December 12, 1947, page 267.

DIABETES MELLITUS IN INFANCY.

THOUGH *diabetes mellitus* is not a rarity among children, its occurrence (or at any rate its diagnosis) in infants during the first year of life is uncommon. J. Schwartzman, Margaret E. Crusins and D. P. Beirne, who have reported a case of the disease detected in a child at the age of seven months,[1] were able to find only 56 other cases reported in the literature. Analysis of these cases substantiates the view that hereditary factors are important in the occurrence of the disease, and it seems that infections are the most common precipitating factor; disorders of the central nervous system have been present in an appreciable number of cases, but their ætiological significance is not always clear. Diagnosis is especially important in this group, and Schwartzman and his colleagues point out that there are certain features which, though not diagnostic, should arouse suspicion, especially if associated with a family history. They are loss of weight and emaciation, tendency to cutaneous involvement, frequent symptoms of infection of the respiratory tract, irritability and crystalline deposits on, or stiffening of, the diapers. The prognosis is greatly affected by the earliness of diagnosis and these investigators advocate a positive approach to ensure early detection. The earlier the onset, the worse the prognosis, and if the child is under the age of three months the outlook is poor; but, apart from this, early recognition and correct treatment bring a good chance of a normal life, at least during the first fifteen or twenty years of life. After that time complications, such as polyneuritis, nephropathy and ocular disorders, are prone to occur, a finding supported by A. L. Chute[2] in a survey of patients treated for *diabetes mellitus* at the Hospital for Sick Children, Toronto, since insulin became available in 1922. Insulin has, of course, completely changed the prognosis of the disease, especially as to survival, though the later occurrence of complications, as already mentioned, has become a problem. There are differences of opinion as to the best therapeutic *régime*, but a good deal of support seems to be given to a diet approaching the normal, supplemented, according to the individual need, with insulin and vitamins. By these means the disease can usually be controlled. The real problem lies in early detection, and for this Schwartzman and his colleagues suggest three procedures. Firstly, in the presence of a family history of diabetes (not necessarily manifest in either parent), routine glucose tolerance tests should be carried out on the child every two months for the first year and every six months thereafter. During infections, daily examination should be made of the urine, with sugar tolerance tests at the onset and the end of the illness. Finally, after any infection, routine urinalysis should be carried out every two weeks for a period of three months, followed by a glucose tolerance test at the end of that time. This is an ambitious programme and it is not likely to be always practicable on the score of expense or available facilities. Nevertheless, it is a positive suggestion and theoretically desirable. Unless something better can be suggested, it might surely be regarded as an ideal at which to aim.

[1] *American Journal of Diseases of Children*, November, 1947.
[2] *American Journal of Diseases of Children*, January, 1948.

Abstracts from Medical Literature.

SURGERY.

Anatomy of the Vagus Nerves.

WALTMAN WALTERS *et alii* (*Archives of Surgery*, October, 1947) review the results of gastric neurectomy in 66 cases at the Mayo Clinic, and discuss anatomical variations in the distribution of the vagus nerves at the lower end of the œsophagus as found in dissections at autopsy in more than 100 subjects. An endeavour was made to determine whether the thoracic or abdominal approach to the lower part of the œsophagus was better. In most instances it was found that, by the time they had reached the œsophageal hiatus, the right and left gastric (vagus) nerves had formed two relatively large trunks, although in most cases their arrangement at higher levels had been plexiform and irregular. Below the diaphragm the nerves ran a remarkably constant course. Walters believes that the best approach to the gastric nerves is by an upper abdominal incision, which permits exploration of the abdomen, examination of the ulcer and its removal if thought malignant. This approach also permits the relief of pyloric or duodenal obstruction if present.

The Appendiceal Stump.

GEORGE H. YEAGER (*Annals of Surgery*, November, 1947) gives the results of his study of the end results of three accepted methods of dealing with the appendiceal stump after appendicectomy as carried out on a series of rabbits. The three methods were: (i) simple ligation, (ii) ligature and inversion, (iii) inversion without ligature. There were 44 experiments—25 with buried stump and 19 with simple ligation. At varying periods (two days, four days, one week and one month) the animals were anæsthetized and the appendiceal stump examined *in situ* and then removed for microscopic study. There was no significant difference in lymph node enlargement with any particular method. There were no abscesses visualized either macroscopically or microscopically. There was greater microscopic inflammatory reaction with the inversion technique, the inflammation being greater with the ligated buried stump than with the unligated buried stump.

Ligature of Arteries.

LAMBERT ROGERS (*The British Journal of Surgery*, July, 1947) discusses the ligature of arteries, with particular reference to carotid occlusion and the circle of Willis. Arteries are ligated either in continuity or with division between ligatures. The second method was first recommended by Celsus, and has certain advantages: recanalization is prevented, peripheral vasospasm is reduced (by division of sympathetic fibres in the adventitia), and secondary hæmorrhage is rendered less likely (since the ends are able to retract). In pre-antiseptic times the danger of secondary hæmorrhage following ligature in continuity was high—50% in Billroth's series. A further advantage of division between ligatures is the avoidance of "pumping action" which carries the risk of displacing a clot and causing embolism. When a main artery is ligated the accompanying vein should also be tied unless pulsation in the distal part of the artery shows that collateral circulation is adequate. Other steps which mitigate the effects on the peripheral circulation of ligation of the main artery of a limb include the following. The ligature should, if possible, be placed just distal to, rather than well below, a large branch, so that the arterial pressure is directed into the branch rather than expended in distending a blind pocket. The metabolism of the limb should be lowered by depressing its temperature by exposure to a draught of cold air, and peripheral vessels relaxed by raising the body temperature with hot blankets *et cetera*. Ligature of the carotids carries special implications because of the danger of interference with the blood supply of the brain. This may occur in two ways: firstly by immediate cerebral anæmia, secondly by thrombosis or embolus secondary to the ligation. Ligation of the common carotid is safer than ligation of the internal carotid because of the collateral pathways available in the former instance. Although by analogy with the circulation in a limb it might be thought wise to tie the accompanying internal jugular vein at the same time, electroencephalography has shown that this step increases cerebral anoxia.

Carcinoma of the Ampulla of Vater.

JOHN MORLEY (*The British Journal of Surgery*, October, 1947) reports six cases of carcinoma of the ampulla of Vater treated by resection of the whole of the second part of the duodenum along with a considerable portion of the head of the pancreas, the pancreatic duct being tied and not anastomosed with the alimentary tract. One patient died as a direct result of operation, another died six weeks after operation, two patients developed liver metastases within twelve months and died, the fifth is ill with ascending cholangitis seven months after operation, and the sixth is well eleven months after operation. The operations were carried out in two stages, cholecystogastrostomy and posterior gastro-jejunostomy being performed at the first stage and the resection at the second stage. The author discusses the subject and points out that Whipple has largely abandoned the two-stage operation for a one-stage procedure. He presents Whipple's arguments in favour of this change and indicates his reasons for his own preference for the two-stage procedure in his own six cases. Finally, he gives some detail of a patient who, apparently, had a carcinoma of the ampulla of Vater and was spontaneously cured. She died of coronary disease twenty years after a laparotomy was performed.

Chronic Eventrations and Large Herniæ Treated by Progressive Pneumoperitoneum.

IVAN GONI MARENO (*Surgery*, December, 1947) describes an original procedure in the treatment of large herniæ and chronic eventrations. In four or five sessions progressive pneumoperitoneum is induced over a period of three or four weeks and in quantities that in the last session may reach extraordinary amounts. The rationale is described as an action upon the disproportion between the abdominal container and its contents, most of which are lodged in the large sac—graphically described as "the second abdomen". Were the distended viscera, omenta, fatty and œdematous mesentery suddenly returned into the abdominal cavity, not only would this produce embarrassment by increasing the abdominal contents, but also the closure of the peritoneum and other parietal layers would be difficult and the sutures would be subjected to excessive tension. Further, the post-operative condition of the patient would be made unsatisfactory by the effects of sudden increase in abdominal tension in a patient whose breathing is already deficient. The technique of the air injection is given in detail and the contraindications to this procedure are discussed.

Medullary Tractotomy for Relief of Intractable Pain.

ALBERT S. CRAWFORD (*Archives of Surgery*, November, 1947) reports his experience in operating on eleven patients with intractable pain in the upper part of the torso due to malignant disease. In nine patients unilateral and in two bilateral medullary tractotomy was performed. In all cases a high level of pain analgesia was obtained. The two patients on whom the bilateral operation was performed died, as did one on whom the unilateral operation was performed. All operations were carried out under local anæsthesia with the patients sitting up in the neurosurgical chair. The side of the medulla was exposed up to the level of the inferior olive. The cut was made into the medulla caudal to the last of the vagal rootlets and cephalad to the last spinal rootlets of the accessory nerve. Special cutting instruments guided the length of the surface cut and the depth of the internal section. With the patient under local anæsthesia the effective level of analgesia could be tested during operation.

Antacids and Mucin in Treatment of Peptic Ulcer.

LEO L. HARDT AND LEONARD P. BRODT (*Archives of Surgery*, November, 1947) record the results of their studies, both clinical and gastroscopic, of the effect of antacids on the gastric mucosa. The medical literature and the advertisements of pharmaceutical companies would indicate that antacids, especially magnesium trisilicate and aluminum hydroxide, have, in addition to their action of reducing acidity, an astringent and protective coating action on the gastric mucosa. The authors observed gastroscopically the physical appearance of aluminum gels, magnesium trisilicate and calcium carbonate in the stomach. These observations were made on 35 patients—fifteen with normal stomachs, three with hypertrophic gastritis, five with atrophic gastritis, nine with duodenal ulcer and three with gastric ulcer. The speed with which antacids left the stomach was variable, and in many cases they were gone from the stomach within twenty to forty-five minutes. This observation was confirmed by X-ray studies in which sufficient barium was added to the antacid to make it visible. The antacids seen gastroscopically were scattered throughout the stomach in clumps of various sizes and could not

be differentiated from one another. None of the antacids gave any distinct coating effect. However, in a few instances where there was increased mucus in the stomach there seemed a slight tendency for the aluminum gels to diffuse through the mucus which adhered to the gastric wall, and to be delayed in their exodus from the stomach. As a result of the above observations the authors then studied gastroscopically and radiologically the appearance of a mixture containing magnesium trisilicate and aluminum hydroxide to which was added 10% to 20% of gastric mucin. Invariably the authors could demonstrate a decided tendency towards coating and filming of the mucosa; and in every case of gastric ulcer the ulcer crater was covered by a pool of antacid mixture and the mucosa around the ulcer by a thick filmy coating. The mixture was observed gastroscopically and confirmed radiologically to be present in the stomach as long as one hour and forty minutes after instillation.

Intestinal Obstruction.

CONRAD J. BAUMGARTNER (*Archives of Surgery*, November, 1947) has surveyed the management in the last five years of acute intestinal obstruction at the Los Angeles General Hospital, and arrived at the following conclusions. The mortality of this condition despite the use of gastric and intestinal siphonage, the intravenous administration of fluids, plasma and blood, and other therapeutic and diagnostic aids, particularly antibiotics and X-ray examinations, remains too high, the major factors being delay in recognizing a strangulated lesion and technical errors. The delay in recognizing strangulating lesions is due in no small part to the calming influence of indwelling siphonage on both the patient and the surgeon. The recent experimental work of Blain and Kennedy at the Johns Hopkins Hospital in the early use of massive doses of penicillin is promising and it is hoped that its use in practice will reduce the mortality rate.

Tetraethylammonium Chloride in Experimental Acute Arterial Insufficiency.

FREDERICK W. COOPER, ROY L. ROBERTSON AND E. W. DENNIS (*Surgery*, November, 1947) describe a series of experiments undertaken to determine the efficacy of chemical sympathetic blockage in experimental acute arterial injuries. As the substance used to produce the chemical sympathetic block they used tetraethylammonium chloride (supplied as "Etamon" by Parke, Davis and Company). The chief action of this drug is to block, at the autonomic ganglia, the transmission of sympathetic and parasympathetic nerve impulses. In a series of thirty dogs, by identical operative procedures on each animal, the terminal aorta was doubly ligated distal to the origin of the inferior mesenteric artery, but proximal to the origin of the deep circumflex iliac arteries. Ligatures were placed around the two external iliac arteries and the common hypogastric trunk. The intervening arterial trunks were excised. In a control group of ten dogs this was all that was done, while in the experimental group administration of "Etamon" was begun immediately in dosage proportional to the body weight. The results were as follows. Nine out of ten of the control animals died, the majority within four days, without evidence of establishment of collateral circulation. In the experimental group, receiving the tetraethylammonium chloride, fourteen out of twenty animals survived, regaining excellent functional activity within two to six days. Arteriograms in control animals showed little filling of collateral channels by contrast media, while in the animals which survived and received tetraethylammonium chloride therapy a graded increase in filling of the vessels could be demonstrated by arteriograms. In view of these experimental results it is suggested that tetraethylammonium chloride may become a valuable adjunct in the clinical treatment of acute arterial injuries involving major vessels.

Periodic Paralysis, Exophthalmic Goitre and 6-Propylthiouracil.

LINDON SEED (*The Western Journal of Surgery, Obstetrics and Gynecology*, December, 1947) reviews the literature on periodic paralysis and describes the progress of a patient with this condition and exophthalmic goitre under treatment with 6-propylthiouracil. Periodic paralysis is a rare condition characterized by periodic attacks of flaccid paralysis accompanied by a drop in serum potassium content. It occurs most commonly as a familial inherited trait, but also occurs sporadically in individuals with no inherited trait. These sporadic cases are found almost entirely in males and have a tendency to be associated with exophthalmic goitre. Shinosaki first called attention to the frequency of thyreotoxicosis in patients with periodic paralysis. He reported 24 patients with periodic paralysis, of whom seven apparently had true Basedow's disease. In well-controlled experiments he showed that attacks could be induced in susceptible individuals by the continued administration of desiccated thyreoid. The symptoms of paralysis in patients with periodic paralysis and exophthalmic goitre can be relieved by an adequate subtotal thyreoidectomy. Seed's patient was first treated with thiouracil with complete relief of symptoms, but symptoms reappeared when medication was suspended. Potassium therapy did not alter his symptoms. He was given 25 milligrammes of 6-propylthiouracil three times daily and his symptoms disappeared. After several months of treatment medication was discontinued to evaluate its effect. Within one week symptoms began to return and an attack of complete paralysis occurred nine days later. With reinstitution of 6-propylthiouracil therapy he again became symptom-free and remained so while under treatment. A prolonged course of 6-propylthiouracil therapy is contemplated to endeavour to effect a cure.

Radioactive Iodine and the Study of Thyreoid Function.

E. B. ASTWOOD AND MALCOLM M. STANLEY (*The Western Journal of Surgery, Obstetrics and Gynecology*, December, 1947) give a preliminary report of investigations to determine whether a practical method could be developed for the diagnosis of borderline cases of hyperthyreoidism and hypothyreoidism for the study of simple or non-toxic goitre and for the study of antithyreoid compounds. They describe the methods used and the interpretations which seem most reasonable at present. The studies were made on 66 normal subjects, some of whom have been used two or three times, and on 20 patients with disordered thyreoid function. A dose of 0·1 millicurie of I^{131} without added carrier was given by mouth and measurements of radioactivity were made with a shielded Geiger counter centred over the anterior aspect of the neck. During the early hours of iodine uptake by the thyreoid gland the curve of increasing concentration was found to approximate a parabola. The slope of the straight line obtained by plotting the increasing radioactivity against the square root of the time in minutes provided an arbitrary numerical expression of the rate of uptake and was referred to as the accumulation gradient. This method of plotting permitted a prediction of the expected course of uptake when frequent measurements were made during the first two or three hours, and it facilitated a study of the influences of iodine, thiocyanate and antithyreoid compounds. The rate at which the thyreoid accumulated iodine in normal people varied widely; the gradient averaged 9·3, but varied between 1·5 and 36·4. Four patients with myxœdema had very low gradients, as did four who received ordinary iodine. Hyperthyreoidism was associated with concentration gradients greater than normal average, but only one of seven patients with hyperthyreoidism had a concentration gradient above the normal range. A single dose of 100 milligrammes of propylthiouracil completely stopped the accumulation of iodine within thirty minutes, and the effect lasted three hours. Larger doses gave a more prolonged inhibition. Propylthiouracil given before the radioactive iodine greatly limited its uptake; the small amount of iodine accumulated under these conditions remained as iodine and was discharged by the giving of potassium thiocyanate and diluted out by the administration of potassium iodide.

Cranioplasty with Ready-Made Acrylic Cranioprostheses.

HUNTER J. MACKAY (*Surgery*, December, 1947) describes the detail of making and using ready-made acrylic cranioprostheses. He considers that the use of acrylic has made cranioplasty an appreciably faster and easier procedure than when tantalum was used. He used acrylic in closing defects in seventeen patients, and in each case it proved satisfactory and æsthetically acceptable. He describes the method of fashioning and inserting onlay and inlay types of prostheses, and considers that the major technical virtues of acrylic for cranioplasty are that its thermoplasticity allows easy and rapid moulding and secondary alteration of basic cranioprostheses; the characteristic transparency permits accurate visual tracing of the skull defects with bone wax; it is readily worked with ordinary instruments; its cementing facility provides for plastic replacement of soft tissue and obliteration of dead spaces. Also, economically, acrylic is readily obtained at a low cost.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at the Children's Hospital, Carlton, Melbourne, on November 19, 1947. The meeting took the form of a series of demonstrations by members of the honorary medical staff of the hospital and was combined with the monthly meeting of the Melbourne Pædiatric Society. Part of this report appeared in the issues of May 22 and May 29, 1948.

Ligation of Patent Ductus Arteriosus.

DR. MEDWYN HUTSON showed a patient to illustrate some points in the diagnosis of patent *ductus arteriosus* and to demonstrate the result obtained after successful ligation. The patient, a girl, had been born in October, 1940; when she was six months of age a loud basal systolic murmur was noted and a congenital lesion of the heart diagnosed. Since then the child had had frequent recurrent attacks of wheezing and a croupy cough, each attack lasting a day or two and occurring every few weeks. Because the father had asthma it was assumed that the attacks had an asthmatic basis. Growth and gain in weight were slow, so that at the age of six years her weight was thirty-eight pounds and her height three feet ten inches. Although she was moderately vigorous and active she tired easily and wheezing was easily provoked after exercise; respiratory infections were frequent. In July, 1946, she reported to the hospital, and examination showed the classical features of patent *ductus arteriosus*. The heart was enlarged, precordial pulsation was prominent, and a continuous thrill was palpable at the base of the heart. Carotid pulsation and the water-hammer type of pulse suggested that regurgitation was occurring, and the blood pressure readings of 105 millimetres of mercury (systolic) and 30 millimetres (diastolic) confirmed this. The characteristic machinery murmur, continuous through systole and diastole, was heard at the pulmonary area, and a soft systolic bruit at the apex. An X-ray examination showed general cardiac enlargement, with broadening of the conus area and some passive congestion of the lung fields. Partial atelectasis of the middle lobe of the right lung was also present, but the lobe had reexpanded in films made two weeks later. Fluoroscopy showed: (i) broadening of the conus, (ii) enlargement of the left ventricle, (iii) possible enlargement of the left auricle, (iv) enlarged hilar shadows, but no hilar dance, and (v) passive pulmonary congestion. Dr. Colin Macdonald had concluded that there was some radiological evidence to confirm the clinical diagnosis.

Operation was decided upon, to take place at a convenient date, and the child was kept under observation. In March, 1947, the tonsils were removed by dissection following upon a series of sore throats. In April, 1947, Dr. Russell Howard exposed the great vessels, and a widely patent *ductus arteriosus* was demonstrated and ligated with tape and double purse-string sutures of silk. The murmur ceased instantly, although the systolic bruit could still be heard at the cardiac apex. Convalescence was delayed a little by a small pneumothorax and loculated effusion in the region of the upper lobe of the left lung, but the patient was able to leave hospital in a few weeks. Post-operatively the blood pressure was 110 millimetres of mercury (systolic) and 70 millimetres (diastolic) and the reduction in the size of the heart, as shown in the X-ray films, was very striking. The cardiothoracic ratio had decreased from from 0·55 to 0·40. Since her discharge from hospital the parents had been very pleased with the child's progress. She had had only one moderate attack of asthma and bronchitis which cleared up rapidly with small doses of iodide and ephedrine with phenobarbital. She had been more vigorous and active, more vivacious in her play and demeanour and had gained eight pounds in weight during five months. The parents were impressed by the absence of the precordial and carotid pulsation and considered that she could now hold her own with other children.

Dr. Hutson stated that the case demonstrated all the usual features of patent *ductus arteriosus* and commented on the difficulty of diagnosis in the first years of life, before the full development of the characteristic murmur. In the present case the enlargement of the heart to such a degree gave rise to a doubt that some other congenital lesion might have been present, but the return of the heart to normal size following ligation of the ductus was very instructive. Attention was drawn to the atelectasis of the middle lobe of the right lung shown by the first X-ray examination and the comment was made that similar lobar lesions were quite common in the respiratory infections of childhood.

Thrombocytopenic Purpura.

Dr. Hutson then presented a girl, aged six years, who had had recurrent manifestations of purpura since the age of nine months. Although she had had constant bruising, frequent crops of petechiæ and numerous epistaxes, there had not been any dangerous episode of bleeding, and the problem remained whether splenectomy should be performed. In July, 1942, at the age of seven months, the patient had had meningococcal meningitis and made an uneventful and complete recovery with sulphapyridine therapy. Soon after that the parents noted that she bruised easily, many bruises occurring without any obvious injury, and that state had continued since. It was very rare for her to be without a dozen bruises, and crops of petechial hæmorrhages occurred from time to time. The first blood examination was made in November, 1944, and then it was found that the bleeding time was ten minutes, the coagulation time four minutes, and very few platelets were seen on a stained film. The ascorbic acid content of the urine was normal. Similar findings had been recorded on various occasions since then and there had been no significant anæmia or changes in the differential white cell count. In October, 1946, her nose was cauterized following repeated attacks of epistaxis, and in May, 1947, she was admitted to hospital with severe epistaxis. At that stage the platelet count varied from 60,000 to 90,000 per cubic millimetre, the bleeding time was estimated at thirteen minutes and the prothrombin index was 100. The Hess capillary resistance test had shown variable results, but there had never been many petechial hæmorrhages produced even on occasions when spontaneous petechiæ were present on the body. Recently, in October, 1947, she had had acute tonsillitis remarkable for the fact that the tonsils were so acutely congested that they were mulberry in colour and a little blood was seen oozing from the surface of both tonsils. The infection subsided rapidly when penicillin was given parenterally. Blood examination showed the hæmoglobin value to be 12 grammes *per centum*, the red blood corpuscles to number 4,000,000 per cubic millimetre, and the white cells 8000 per cubic millimetre; of the latter 58% were neutrophile cells, 8% eosinophile cells, 1·5% basophile cells, 23% lymphocytes and 4% monocytes. The platelets numbered 39,000 per cubic millimetre. Films of marrow obtained by sternal puncture showed a normoblastic and active proliferation of red cells, and the differential count was within usual limits except that the proportion of eosinophile cells was slightly increased. The megakaryocytes appeared to be present in normal numbers and exhibited a morphology said to be characteristic of thrombocytopenic purpura, in that there was an absence of budding off of platelets, as described by Dameshek and Miller. Dr. Hutson said that he was indebted to Dr. Colebatch for the report on the blood.

Dr. Hutson then went on to say that the girl presented the typical picture of thrombocytopenic purpura, with a consistently low platelet count, a prolonged bleeding time and a normal coagulation time. The condition was manifested by very pronounced and persistent bruising, occasional crops of petechiæ and occasional bleeding. Although defective capillaries were said to play an important part in the production of purpura, it was interesting to note that the Hess test did not produce conclusive results. The condition had lasted too long for it to be due to the onset of some leuchæmic process or other symptomatic cause of thrombocytopenia, and its duration and the otherwise good clinical state of the patient made a toxic cause very unlikely. The possibility of an allergic basis had still to be considered, and Schwartze had stated that the results of splenectomy were not satisfactory if eosinophilia was disclosed in the marrow smears. On the other hand the megakaryocytes presented the picture seen in idiopathic purpura. The weight of evidence was therefore in favour of the last-mentioned diagnosis and splenectomy had been under consideration for some time. Since there had been no very serious interference with her progress so far they had been loath to proceed, although the danger of a sudden acute phase with extensive or internal bleeding had to be considered. The records of the Children's Hospital gave very little help in that respect as the mortality with and without splenectomy seemed to be much the same. It was certainly true that splenectomy might be dangerous in an acute phase and chronic conditions such as the one under consideration were difficult to compare. Wintrope stated that the prognosis with operation was such that three out of four subjects might be expected to do well if treated after

the first bleeding episode, and that 50 did well if treated after severe attacks.

Dr. Hutson said that it was not intended to discuss the difficult question of ætiology in detail. It was apparently certain that the spleen had some effect; whether it was by destruction of circulating platelets or by some indirect inhibiting effect on the maturation of platelets could not be stated. Dameshek claimed that the increased production of platelets by budding from the megakaryocytes could be demonstrated within twenty-four hours of splenectomy. The part played by abnormality in contractility of the capillaries was not clearly defined.

The Surgery of Trauma.

DR. MURRAY CLARKE showed several patients illustrating the surgery of trauma. His first patient, a girl, aged two and a half years, had lost most of the skin and soft tissues of the dorsum of the right foot in a motor car accident, tarsal bones and ankle joint being exposed. A compound fracture of the right tibia and fibula was present in the mid-shaft region. Amputation was avoided by grafting a direct flap of skin and subcutaneous fat from the opposite calf, the new defect being immediately closed by a split-skin graft. The fractures were immobilized by two wires at right angles to each other. At the time of the meeting the child was walking with no apparent disability.

Dr. Clarke's second patient, a boy, aged eight years, had been accidentally shot in the right axilla, the bullet passing between the cords of the brachial plexus causing minimal macroscopic damage and completely severing the axillary artery. After operation the arm, which was cold, white and pulseless, was packed in ice to lower the metabolism and oxygen requirements of the part until collateral circulation was established. After four days the arm was removed from the ice and the circulation slowly improved. At the time of the meeting, six months later, although no pulse could be felt, the circulation appeared practically normal and the injury to the radial, median and ulnar nerves had recovered, the only disability being in the interossei, the lumbricals and the *flexor pollicis longus*.

The third patient, a girl, aged seven years, who had been severely burnt on both arms and chest some years previously with very slow healing, had suffered from the disability of having her arms fixed to her sides by strong fibrous bands. That was completely relieved by a series of "Z" rearrangements of skin and scar tissue.

The last patient shown by Dr. Clarke was a boy, aged twelve years, who had had a traumatic amputation of most of his thumb. The wound had been closed and subsequent disabling infection avoided by the use of an immediate direct abdominal flap.

DR. RUSSELL HOWARD showed a series of patients illustrating the treatment of fractured neck of the femur and of slipped capital femoral epiphysis by introduction of the Smith-Peterson nail; the treatment of simple and compound fractures of the upper third of the femoral shaft by the use of intramedullary nails; the treatment of other simple and compound fractures of the femur, tibia and humerus by application of vitallium plates. He explained the changed outlook towards the use of internal fixation in compound fractures since the appearance of penicillin in the surgeon's armamentarium. Primary skin union was now the rule and it was usually wise to take advantage of the exposure of the bone by effecting internal fixation, thus ensuring perfect position and immobilization.

(To be continued.)

Post-Graduate Work.

LECTURES ON CHILD HEALTH BY PROFESSOR J. C. SPENCE.

PROFESSOR J. C. SPENCE, M.D., F.R.C.P., Nuffield Professor of Child Health, University of Durham, Newcastle on Tyne, will be visiting Australia on a lecturing tour in July, August and September of this year.

Professor Spence is a member of the Medical Research Council and also a member of the University Grants Committee, and was appointed in 1942 to the first Nuffield Chair of Child Health in the United Kingdom. Prior to 1942 he was a general consulting physician to the Royal Victoria Infirmary, Newcastle, but in addition he played a large part in pædiatric medicine and teaching. He has always had a deep interest in and a close contact with children, and as far back as 1932 he commenced a unit in which the mother and baby were admitted together for treatment, so that the mother could conduct the nursing of her sick child. This rather unique experiment has stood the test of time and it is now one of the most interesting of the features of his department.

Professor Spence has one of the most active departments of child health in the United Kingdom at the present time. He is a man of vision and ideas and his thinking and practice of medicine are strongly influenced by two predominant concepts. The first of these is the humanitarian approach to the sick patient and the second is the importance of social factors in health and sickness. These concepts are very clearly reflected in the work of his department, especially in teaching his students and in his research programmes. He has much to give to Australian medicine, notably in his ideas on teaching, on the social aspects of disease and health and the function of a university department in a teaching hospital. His lecturing tour has been arranged by the post-graduate committees in medicine of the several States. He will visit Sydney and Brisbane in July, Adelaide and the Australasian Medical Congress (British Medical Association) in Perth in August, will then proceed to Tasmania, and will conclude his tour in Melbourne in September. In July he will also take part in a seminar on child health in Canberra. Detailed programmes will be published later.

Organization of the tour is in the hands of the Melbourne Permanent Post-Graduate Committee, 426, Albert Street, East Melbourne.

AN INTERNATIONAL COURSE ON SOCIAL MEDICINE.

POST-GRADUATE courses on social medicine are being arranged in England by the National Council for the Rehabilitation of Industrial Workers. The courses are intended for medical practitioners and social workers concerned with environmental factors in individual and group health. The courses will be held at Roffey Park Rehabilitation Centre, Horsham, Sussex. Four courses have been arranged—from June 28 to July 4, from July 26 to August 1, from August 9 to August 15, and from August 23 to August 29. The programme in the four courses will be identical. The fee, inclusive of tuition, residence and social activities, is twelve guineas. Further information may be obtained from the Secretary, Roffey Park, Horsham, Sussex, England.

Correspondence.

PROGNOSIS IN BREAST CANCER.

SIR: In a recent number of the journal (March 27, 1948) your current comment upon "prognosis in breast cancer" opens with the statement that cancer of the breast is still the *commonest* form of cancer in the human subject. (The italics are mine.) Is this just a slip of the pen or do world statistics justify such a statement concerning the anatomical distribution of cancer?

In this country, as in others, it is certainly wise to emphasize the relatively high frequency of breast cancer and to denominate this affliction as "a target of great importance in the campaign against malignant disease"; nevertheless, on the ground of frequency alone, this "form" of cancer is not of pre-emptive statistical significance in the State of Victoria. It ranks second to cancer of the skin in our morbidity tables and third or fourth in the official mortality bills.

In the absence of statutory notification of cases of cancer, the Victorian Government Statist does not issue morbidity tables, but our morbidity sample figures may be regarded as reasonably representative. In Table I is given a conspectus of the overall cancer experience of six metropolitan public hospitals during 1940, 1941, 1946 and 1947, arranged according to a systemic classification. Further analysis of Table I, with a view to "seeding" of particular organs, discloses top-ranking frequencies as follows: skin (excluding lip, scrotum, vulva, anus), 1683 cases (22·5%); breast, 870 (11·6%); large intestine (including rectum), 784 (10·5%); uterus, 643 (8·6%); stomach, 533 (7·1%); prostate, 243 (3·2%).

Turning now to mortality statistics, we find a radical change in the relative frequency of items as listed in the

TABLE I.

Systemic Classification.	1940.		1941.		1946.		1947.		Total.
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	
I. Buccal cavity and pharynx	145	35	188	40	140	39	133	28	748
II. Digestive organs	250	162	265	153	261	174	241	161	1667
III. Respiratory organs	55	15	60	15	72	25	73	18	333
IV. Female genital organs	—	201	—	217	—	189	—	245	852
V. Breast	2	219	2	224	—	215	1	207	870
VI. Male genital organs	74	—	81	—	68	—	76	—	299
VII. Urinary organs	31	15	44	10	50	27	54	19	250
VIII. Skin	263	190	251	170	260	190	209	150	1683
IX. Nervous system and eye	34	25	31	16	53	30	44	30	263
X. Miscellaneous	34	58	47	39	83	52	118	83	514
Total	888	920	969	884	987	941	949	941	7479

morbidity table. The ranking order as a cause of death is, first, stomach (one in four cancer deaths); then large intestine and rectum (one in six); and then breast (one in nine).

A comparison of mortality and morbidity rankings, therefore, bears out your remark that "there are grounds for encouragement in this particular field [cancer of the breast] in regard to the results of treatment". This, of course, is your main theme, namely, the prognosis of surgically treated breast cancer—and any criticism thus far offered does not in the least detract from its significance. The study upon which your commentary was based is of considerable interest and importance in that it sets out to discover what eventually happens to women *after* having survived radical mastectomy by at least five years. It was surprising to find how often late metastases developed after many years of apparent good health. Although we, in Melbourne, cannot as yet contribute follow-up data on this point, nevertheless the five-year survival rates of the 1940-1941 sample are available and may be matched with the American figures (Table II).

TABLE II.

Comparative Five-year Survival Rates in Breast Cancer Surgically Treated.

Sample.	Total Surgically Treated.	Completeness of Follow-up.	Five-year Survivors.	
			Number.	Percentage of Total Operated.
Six public hospitals, Melbourne (1940–1941)	247	97%	115	46·6
Henry Ford Hospital, Detroit (1930–1941)	412	99%	177	43·0
Combined	659	—	292	44·3

As regards the effect of post-operative irradiation on prognosis, the Melbourne sample may be divided into a subgroup of 148 cases given post-operative X-ray therapy and a second subgroup of 99 cases not so treated. The respective five-year survival rates prove to be 46·6% in the former and 46·5% in the latter.

Yours, etc.,

ROBERT FOWLER,
Honorary Chief Registrar.

Anti-Cancer Council of Victoria,
C.o. Royal Australasian College of Surgeons,
Spring Street,
Melbourne, C.1.
April 15, 1948.

THE PHARMACEUTICAL BENEFITS ACT.

SIR: We are amazed at the implications of the regulation gazetted today regarding the penalty for "disposal" of government prescription forms and formulary.

We intend to safeguard ourselves by sealing these documents as soon as they are issued to us, and depositing them in the vaults of our respective banks. We would commend this course of action to all those who wish to avoid the humiliation of being fined or gaoled should these documents be found to have been mislaid when the government authority demands their production.

Yours, etc.,

W. K. MCINTYRE, R. GODFREY-SMITH, R. P. BOOTH, G. T. H. HARRIS, W. R. MOLONEY, D. P. CHURTON, ROBERT WALL, H. J. C. ENGISCH.

Launceston,
Tasmania,
May 13, 1948.

SIR: Now that the profession as a whole has reached the stage of concerted action in the struggle against the free medicine bill, I consider that it would help very greatly if the practitioners in every town and suburb in the Commonwealth compared notes, so that any waverer in their own particular group may be known to them all.

Should a waverer be found, his own friends and colleagues who meet him and work with him daily should show him the need for falling in line with his fellow practitioners who are standing loyally by one another and by their association.

We know what members of a Labour Government think of a unionist who fails to support his comrades in an industrial dispute, and yet it seems that this so-called Labour Government is hoping to find such men in our ranks.

The unanimous and determined opposition which was apparent to me at a recent Branch meeting augurs badly for the Government's chances of success, and if every member will regard it as his personal duty not only to discover any waverer in his own immediate vicinity, but also to convert him to the ideals for which our association is fighting, the possibility of defeat will be very remote indeed.

Yours, etc.,

JAMES A. LAWSON.

Harrow Road and Mary Street,
Auburn,
New South Wales.
May 21, 1948.

SIR: The shouting and the tumult, hopefully, will have died by the time this has been published; perhaps calm reflection, logical thinking and tolerance will achieve, possibly by conciliation, those things which stubbornness cannot and never will.

Has anyone ever paid particular attention to these portions of an act of the State of New South Wales?

> 20. (1) For the purpose of preventing the improper use of the drugs to which this Part of the Act applies the Governor may by regulations make provision for the regulating . . . and in particular . . . for
>
> (*c*) regulating the issue by medical practitioners . . . of prescriptions containing such drug . . .
>
> (*g*) providing that any specified breach of the regulations shall be regarded as "infamous conduct in a professional respect".
>
> (3) Any person
>
> (*a*) who acts in contravention of or fails to comply with any regulation made under this part of this Act; or (*b*) . . . shall be guilty of an offence against this Part of this Act.
>
> 20b. (1) Every person guilty of an offence against this Part of this Act shall in respect of each offence

be liable on summary conviction to a fine not exceeding four hundred pounds or to imprisonment with or without hard labour for a term not exceeding two years, or to both such fine and imprisonment.

Or to these portions of the corresponding regulations?

11. (1) The holder of a licence . . . and any other person who may, in the ordinary course of his profession . . . dispense, or compound, or use drugs . . . shall keep, or cause to be kept, a register . . . of the drugs . . . or used by him . . .

17. (2) Where a medical practitioner . . . issues a prescription he shall comply with the following conditions:

(*a*) The prescription shall be in writing, shall be dated . . . and shall clearly indicate the maximum number of times such prescription shall be dispensed.

25. (1) Where a person . . . has been convicted of any offence against the Act or the Regulations, the Minister may withdraw the authority . . .

(4) Where such person . . . is a medical practitioner such person shall not issue a prescription for a drug . . .

The foregoing are excerpts from the *Police Offences (Amendment) Act*, 1908, and its regulations of the State of New South Wales. "This Part of this Act" refers to Part 6 of the act.

As the Federal Council to some extent objects to *The Pharmaceutical Benefits Act* on the grounds that the penal clauses of the act's regulations are objectionable to the medical profession, in my opinion it is reasonable to ask the following questions.

1. Has the New South Wales Branch ever objected to the penal clauses of the *Police Offences Act*—£400 and/or two years' hard labour?
2. Has the State Government ever during the past forty years abused its regulation-making power under the act?
3. Have the authorities ever abused their powers granted to them by the regulations?
4. Are not these powers solely used for the purpose of preventing the abuse of privileges by medical practitioners?
5. And are they not only used when such privileges are abused?

Yours, etc.,

C. H. JAEDE.

Mascot,
New South Wales,
May 25, 1948.

SIR: It seems incredible that, in the year 1948, the best forms of propaganda which the British Medical Association can devise are the distribution of handbills and the writing of communiques for newspapers. Organizations of far less standing than our association find it necessary to use the radio, the newspaper and the screen for publicizing their points of view.

There are three things which must be done to gain adequate public recognition of our stand on the Commonwealth Government's *Pharmaceutical Benefits Act*. Firstly, we must conduct an intensive radio campaign against the scheme as it now stands. Secondly, full-page displays in every major newspaper in the country should give publicity to our views. Thirdly, we should have slides or a short moving picture on the subject made for showing at all main theatres in all capital cities.

These measures would involve a heavy cost, but a levy of a guinea per member should suffice.

One further point which I wish to make is that, if we believe our cause is morally right, the time for action is now.

Yours, etc.,

CYRIL SWAINE.

21, Miller Street,
North Unley,
South Australia.
May 25, 1948.

Public Health.

ROCKEFELLER FOUNDATION FELLOWSHIPS IN PUBLIC HEALTH.

DR. A. J. METCALFE, Director-General of Health, Commonwealth Department of Health, writes that he has received a letter from Dr. George K. Strode, Director of the International Health Division of the Rockefeller Foundation, in regard to the training of young men to become competent in the field of public health in Australia through the instrumentality of the Foundation's fellowship programme. During conversations with Dr. Metcalfe some months ago in New York Dr. Strode said that the International Health Division of the Rockefeller Foundation would be willing to cooperate in the training of men. Dr. Strode has arranged that Dr. Charles N. Leach, Assistant Director of the International Health Division, shall visit Australia with a dual objective: (i) To gain first-hand impressions of the present state of public health in Australia and to note the trends of development. (ii) To meet and talk with such fellowship candidates as Dr. Metcalfe may wish to propose. It is a rule of the Rockefeller Foundation that before a fellowship grant can be considered the individual must be seen by one of its field representatives. Dr. Leach will fly from San Francisco and is scheduled to arrive in Sydney on July 9, 1948. He plans to spend about three weeks in Australia, and would like to meet prospective fellowship candidates during the first days of his stay. Any young medical practitioner who is interested is invited to communicate as soon as possible with Dr. Metcalfe at the Department of Health, Canberra.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 73, of May 6, 1948.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force: Medical Branch.

The appointment of Temporary Squadron Leader R. K. Doig (257656) is terminated on demobilization, 16th March, 1948.

Reserve: Medical Branch.

The following ex-officers are appointed to commissions with the ranks indicated: Temporary Squadron Leader Ronald Keith Doig (257656), 17th March, 1948; Flight Lieutenant David Arthur Brown (264262), 1st March, 1948.

Ex-Flight Lieutenant William Gowan Norman (283250) is appointed to a commission with the rank of Flight Lieutenant, 1st April, 1948.

The appointment of Flight Lieutenant F. J. Scanlan (267791) is terminated, 27th November, 1945.

The Royal Australasian College of Physicians.

ANNUAL MEETING.

THE annual meeting of the Royal Australasian College of Physicians will be held at Brisbane from June 10 to 12, 1948.

The first scientific session will be held at the main lecture theatre of the Medical School, Herston, at 2.45 p.m. on June 10. The following papers will be read: "Geographical Aspects of Medicine", by Professor D. H. K. Lee; "Histoplasmosis with Biopsy Findings", by Dr. E. H. Derrick; "Modern Conceptions in Hepatic Pathology", by Professor A. J. Canny; "Some Aspects of Renal Function and their Clinical Significance", by Dr. L. D. Walters.

The second scientific session will be held at the same place at 2.15 p.m. on June 11. The following papers will be read: "Precordial Leads in Coronary Disease", by Dr. Ellis Murphy; "Some Causes of Malnutrition", by Dr. P. J. Parsons, Dr. Ian J. Wood and Dr. N. Turner; "Some Physiological Aspects of Psychosomatic Disorders", by Dr. H. R. Love; "Arteriosclerosis following Chronic Plumbism in Queensland Children", by Dr. Jarvis Nye; "Aspects of Lead Nephrosclerosis: (*a*) Estimation of Lead in Bone, (*b*) Histology of Renal Changes", by Dr. E. H. Derrick.

The Annie B. Cunning Lecture will be given at the Brisbane Boys' Grammar School, Gregory Terrace, Brisbane, at 8.15 p.m. on June 11 by Professor S. M. Wadham, Professor of Agriculture in the University of Melbourne.

A clinical meeting will be held on Saturday, June 12, at 9.45 a.m. in the main theatre of the Medical School.

Congress Notes.

AUSTRALASIAN MEDICAL CONGRESS (BRITISH MEDICAL ASSOCIATION).

THE Executive Committee of the sixth session of the Australasian Medical Congress (British Medical Association) to be held at Perth on August 15 to 21, 1948, announces that the following arrangements have been made with Australian National Airways for air travel from Sydney in connexion with the congress.

Twenty seats will be reserved on the "Skymaster" leaving the Kingsford Smith Airport, Mascot, at 7.35 a.m. on August 14; ten seats will be reserved on August 13. Intending members of congress who wish to travel by the A.N.A. service are advised to book without delay. Bookings should be made with the itinerary officer at the A.N.A. office, Martin Place. Members should make their return bookings at the same time. Seats will be held on planes leaving Perth on Saturday night, August 21, and on Sunday night, August 22. Baggage allowance for members of congress (but not for their wives) has been raised for this congress to 45 pounds.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Hull, John Poole, provisional registration, 1947 (Univ. Sydney), 290, Burwood Road, Burwood.

Jackson, Kenneth Charles, provisional registration, 1947 (Univ. Sydney), St. George Hospital, Kogarah.

Obituary.

JOHN KERR.

WE regret to announce the death of Dr. John Kerr, which occurred on May 21, 1948, at Wollongong, New South Wales.

Notice.

A LECTURE on the clinical application of penicillin and streptomycin will be given by Lady Florey to the Resident Medical Officers' Club of the Royal Melbourne Hospital on June 23, 1948, at 8 o'clock p.m. The lecture will be given in the main lecture theatre of the hospital. An invitation to be present is extended to members of the British Medical Association.

Books Received.

"Oxford Essays on Psychology", by William Brown, D.M. (Oxon.), D.Sc. (London), F.R.C.P.; 1948. London: William Heinemann (Medical Books), Limited. 7¼" × 5", pp. 156. Price: 10s. 6d.

"A Primer in Clinical Science", by R. Douglas Wright, 1948. Melbourne: Melbourne University Press. 8½" × 5½", pp. 44. Price: 3s. 6d.

"Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior", by Wendell Muncie, M.D.; Second Edition; 1948. St. Louis: The C. V. Mosby Company; Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9½" × 6½", pp. 620, with illustrations. Price: 67s. 6d.

"Sexual Behavior in the Human Male", by Alfred C. Kinsey, Wardell B. Pomeroy and Clyde E. Martin; 1948. Philadelphia and London: W. B. Saunders Company. 9¼" × 6", pp. 820. Price. 46s.

"Human Physiology", by F. R. Winton, M.D., D.Sc., and L. E. Bayliss, Ph.D.; Third Edition; 1948. London: J. and A. Churchill, Limited. 9¼" × 6", pp. 608, with many illustrations. Price: 25s.

"Standard Radiographic Positions", by Nancy Davies, M.S.R., C.T., and Ursel Isenburg, M.S.R.; Second Edition; 1947. London: Baillière, Tindall and Cox. 8½" × 6½", pp. 232, with many illustrations. Price: 21s.

"Text-book of Public Health" (Formerly Hope and Stallybrass), by W. M. Frazer, O.B.E., M.D., Ch.B., M.Sc., D.P.H., and C. O. Stallybrass, M.D. (State Medicine), Ch.B., D.P.H., M.R.C.S., L.R.C.P., Order of St. Sava; Twelfth Edition; 1948. Edinburgh: E. and S. Livingstone, Limited. 8½" × 5½", pp. 582, with many illustrations, some of them coloured. Price: 30s.

Diary for the Month.

JUNE 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JUNE 10.—Victorian Branch, B.M.A.: Organization Subcommittee.
JUNE 11.—Queensland Branch, B.M.A.: Council Meeting.
JUNE 14.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
JUNE 15.—New South Wales Branch, B.M.A.: Medical Politics Committee.
JUNE 16.—Western Australian Branch, B.M.A.: General Meeting.
JUNE 17.—New South Wales Branch, B.M.A.: Clinical Meeting.
JUNE 17.—Victorian Branch, B.M.A.: Executive Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute; Brisbane City Council (Medical Officer of Health). Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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